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THE UNIVERSITY OF ALBERTA

THE EFFECTS OF A SPECIFIC WEIGHT-TRAINING EXERCISE PROGRAM AND HORMONE REPLACEMENT THERAPY ON BONE MASS IN HEALTHY POSTMENOPAUSAL WOMEN

BY

C. L. THORVALDSON

(C)

A THESIS

SUBMITTED TO THE FACULTY OF GRADUATE STUDIES AND RESEARCH

IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE

OF MASTER OF SCIENCE

DEPARTMENT OF PHYSICAL EDUCATION AND SPORT STUDIES

EDMONTON, ALBERTA

SPRING 1990

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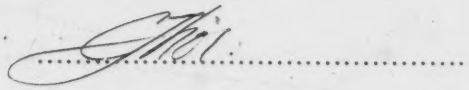

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The undersigned certify that they have read, and recommend to the Faculty of Graduate Studies and Research for acceptance, a thesis entitled THE EFFECTS OF A SPECIFIC WEIGHT-TRAINING PROGRAM AND HORMONE REPLACMENT THERAPY ON BONE MASS IN HEALTHY POSTMENOPAUSAL WOMEN submitted by C. L. THORVALDSON in partial fulfillment of the requirements for the degree of MASTER OF SCIENCE.

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Abstract

This thesis presents interim data on a 2-year study of the relative effects of a specific, weight-training program, and of hormone replacement therapy (HRT) on rate of bone mass loss in 50 women, age 50 to 57 years, and 1 to 5 years after menopause. Trabecular bone density (TBD) at the distal radius, and bone mineral density (BMD) in the lumbar spine and proximal femur were measured. Three subject groups were established: (1) control (n=21); (2) exercise (n=12); (3) HRT (n=17). All groups were standardized on 1500 mg calcium per day by supplementation if required.

The control and exercise groups were established by random assignment of subjects; subjects were allocated to the HRT group after a decision upon HRT (route of administration and amount) was made by the subjects in consultation with their personal physicians.

Subjects exercised at home up to 5 times each week; the duration of each exercise session was 30 to 45 minutes including warm-up. Legs were exercised using a custom designed apparatus; commercial hand-held weights were used to load the arms.

Baseline values for all experimental parameters were not significantly different across study groups. At the time of interim analysis the study had been underway for one year with exercise performed for only 6 months. No significant changes in either TBD or BMD were detected in either the exercise or control groups at this point in the study. The HRT group showed a significant increase in TBD at the distal radius after 12 months of HRT treatment, however, no changes were observed with BMD at either the proximal femur or lumbar spine in this group.

Interim data analysis suggests that HRT treatment is effective in reducing the rate of bone loss at the distal radius, and while not significantly different after 6 months of exercise training, the trend indicates an increase in TBD at the distal radius for the exercise group.

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List of Abbreviations

1, 25 (OH) D	one, twenty-five hydroxy vitamin D
1, 25 $(OH)_2$ D	one, twenty-five dihydroxy vitamin D
1α, 25$(OH)_2$ D	one alpha, twenty-five dihydroxy vitamin D
ANOVA	Analysis of variance
AST	Aspartate aminotranferase
BMC	Bone mineral content
BMD	Bone mineral density
CSTF	Canadian standardized test of fitness
CV	Coefficient of variation
cyclic AMP	Cyclic adenosine monophosphate
DER	Dual energy radiography
DHEA	Dehydroepiandrosterone
DHEAS	Dehydroepiandrosterone sulfate
DPA	Dual photon absorptiometry
FSH	Follicle stimulating hormone
γ-CT	Gamma-ray computed tomography
HRT	Hormone replacement therapy
INVAA	*in-vivo* neutron activation analysis
LD	Lactate dehydrogenase
mSv	milliSievert
PTH	Parathyroid hormone
QCT	Quantitative computed tomography
QDR	Quantitative digital radiography (same as DER)
RM	Repetition maximum
RNI	Recommended nutrient intake for Canadians

ROI	Region of interest
SHBG	Sex hormone binding globulin
SOS	Sum of skinfolds
SOTS	Sum of trunk skinfolds
SPA	Single photon absorptiometry
TBD	Trabecular bone density
VO_2max	Maximal oxygen consumption
W	Watts
WHR	Waist to hip ratio

Chapter 1: Introduction and Literature Review

1.1 Introduction

Depletion of mineral content in the skeleton occurs over several decades before bone fragility leads to fracture with minimal trauma. Physical activity level, particularly during the skeletal growth period (i.e. up to approximately 18 years), and prior to skeletal maturity (i.e. 30 to 35 years) can influence bone mass in the long term and hence the risk of fractures. However, the effects of exercise on bone mass in older adults, and particularly postmenopausal women is not yet established.

Increased emphasis has now been placed on the relationship between age-related bone loss and the risk of diseases, such as osteoporosis. This heightened societal awareness with respect to skeletal diseases results from the cost impact on our health care system, and the increasing proportion of seniors in our population.

Osteoporosis is characterized by a decrease in the quantity of bone, without loss of bone quality, which leads to increased bone porosity and a decreased resistance to fracture such that normal everyday activities (e.g. lifting a bag of groceries) may result in fractures. Clinically, osteoporosis has been defined as bone atrophy with at least one fracture, most commonly a vertebral compression fracture (Remagen, 1989). Osteopenia, on the other hand, is defined as decreased bone mass without fractures. Thus a person with osteoporosis is osteopenic, however, a person who is osteopenic does not necessarily have osteoporosis.

Morbidity and mortality resulting from osteoporotic fractures are increasing in proportion with our aging population and increased life expectancy. Osteoporosis is now recognized as a major health problem which will increase in importance over time. The population at greatest risk for this disease are women beyond the menopause; the prevalence of osteoporotic fracture in women over 65 years of age is now 35-40%

(Remagen, 1989). In Canada 6.5% of the female population is now aged 65 years and older; in 22 years (2011), using population projections, this proportion will be approximately 9.2% (Statistics Canada, 1989).

Over a period of 40 to 50 years many women lose up to half of their skeletal mass, while men lose only 20% to 30% (Peck et al., 1987). Immediately after attaining peak levels in the fourth decade bone is lost at a rate of 0.25% to 1% per year in both men and women. Women usually experience an accelerated bone loss of between 2 to 3% per year around the perimenopausal period (50 to 55 years) which generally continues for 5 to 10 years after menopause. It is widely accepted that this accelerated bone loss results from decline in endogenous estrogen production with ovarian failure, and estrogen replacement therapy has been successfully used to prevent this bone loss. For an individual the potential for excessive bone loss, and hence the future risk for osteoporosis, is dependent on several factors including: the idiopathic decrease in bone mass associated with aging, the menopausal acceleration of bone loss, and the functionality of the skeletal repair mechanism.

The physical and emotional costs of osteoporosis are considerable. Pain results from crush fractures in the spine, and accumulation of such fractures leads to physical deformity (Dowager's hump), and compromised respiratory and digestive function. As a consequence of these factors activity is often limited, leading to further bone loss, decreased independence and self-worth, and often a failure of social networking. The economic impact on the Canadian health care system for treatment and long-term care of fractures associated with bone fragility is estimated to be $700 to $1000 million for 1987 (Phillips et al., 1988). The present and potential future cost to society for osteoporosis requires that various therapies to prevent bone loss be investigated with some urgency.

A number of osteoporosis therapies have been studied over the past decade but to date none have been successful in producing sustained gains in bone mass. Prevention is therefore the best form of treatment.

Skeletal atrophy is also caused by lack of mechanical usage (e.g. physical inactivity or no gravity). Prolonged bed rest and space travel quickly results in loss of bone mass, however, this loss is reversible upon early resumption of activity or return to earth. Conversely, bone hypertrophy occurs with individuals regularly engaged in physical activity. Research has therefore been directed to test physical activity as a prophylactic, and as a therapeutic measure for reduction in bone loss particularly in postmenopausal women. Physical activity has been, and is presently being used to prevent bone loss and to rehabilitate individuals with osteoporosis. However, data is not yet available concerning appropriate type, or amount and intensity of exercise necessary to support this concept.

The work described in this thesis concerns a comparison between physical activity and hormone replacement therapy as therapeutic modalities to reduce bone loss in postmenopausal women. In particular, a specific bone-directed weight-lifting exercise program has been employed, and its effects on bone mass measured and compared with hormone replacement therapy and with a control group not receiving hormone replacement therapy. Preliminary results are presented from an on-going two year pilot clinical investigation.

1.2 History

Osteoporosis is a "modern" disease only to the extent that its prevalence now has a significant economic impact on our health care system. In earlier times (1850) osteoporosis was not a problem to society since life expectancy of women was less than 50 years. Considering, however, that life expectancy today is 80 years (Statistics Canada, 1987), women are now spending more years in their non-reproductive phase then in their reproductive, child-bearing phase of life (Figure 1.1). With a high rate of bone loss primarily occurring at the time of menopause (i.e. approximately 52 years) in

addition to age-related bone loss, the increased incidence of osteoporosis in women becomes apparent.

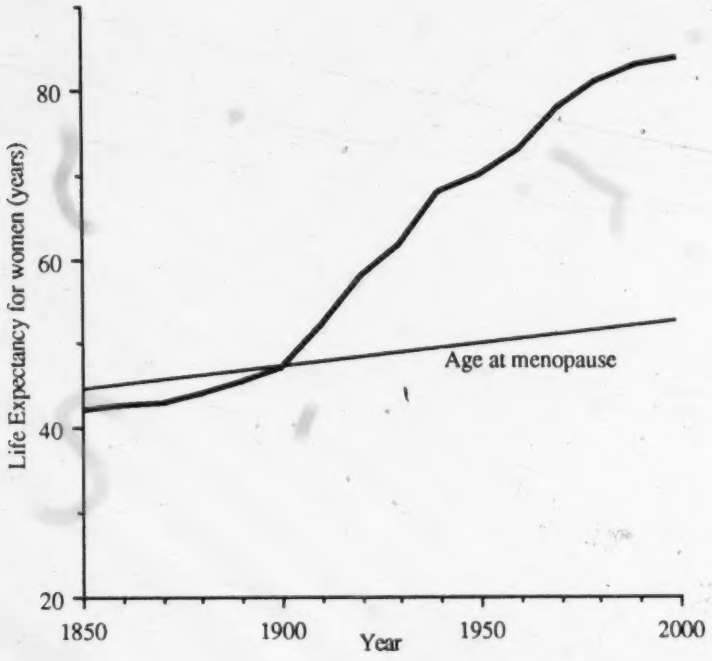


Figure 1.1 Changes in life expectancy. Age at menopause

Medical knowledge concerning skeletal biology has been developed only over the last century. During the nineteenth century various details of skeletal structure, functions and growth patterns were described; however, osteoporosis was uncommon, and when a case occurred it was thought to be a part of the normal aging process. Osteoporosis has a relatively short history, only being recognized over the last 65 years. Some of the first documented medical literature relating to osteoporosis was cited in the early 1800s. Sir Astley Cooper, in 1826, described the bone of elderly fracture victims as "thin in their shell and spongy in their texture". In 1847, Smith, an Irish physician known for Smith's fracture (at the lower radius) described a female patient as "diminishing away in stature until she was reduced to about two thirds of her former height. The vertebrae were greatly atrophied, much diminished in vertical height and deeply excavated in front."

(Karpas et al., 1987). However, it was not until 1940 that osteoporosis was placed onto the "modern scientific map" by a physician and clinical investigator named Fuller Albright, who is regarded as the "father of osteoporosis" (Nordin, 1987).

Prior to 1960 the major limitation to progress of osteoporosis research was bone mass measurement technology — the lack of ways to easily and accurately measure bone mass in-vivo. Before the development of quantitative bone mass measurement techniques the only way to define osteoporosis was from a fracture (usually vertebral). Generalized bone loss could be observed on a standard radiograph (x-ray), however, this form of evaluation could only be made when the total bone mass was reduced by more than 40% — almost half of the skeleton. Thus, in earlier times, with the inability to diagnose or monitor bone loss, the definition of osteoporosis adopted was based upon the existence of fractures (vertebral) and unfortunately still remains today. However, this situation is slowly changing as high precision, quantitative measurements of bone mass become available, high risk subjects can be identified, before "osteoporotic" fractures occur.

No therapeutic efforts to prevent bone loss were implemented prior to 1925 (Frost, 1981). Treatment attempts in the period 1925 to 1980 utilized: sex hormones (particularly estrogens); parathyroid hormone; dietary supplementation of calcium, phosphorus, magnesium, vitamin D and its metabolites; and the somatotropic hormones, somatomedin and calcitonin. However, all attempts to consistently restore bone mass in the osteoporotic skeleton have been unsuccessful to this time. Current therapeutic approaches include: calcium; vitamin D; fluoride, and estrogen. Estrogen replacement therapy has been demonstrated to maintain bone mass but results from most therapies are inconclusive.

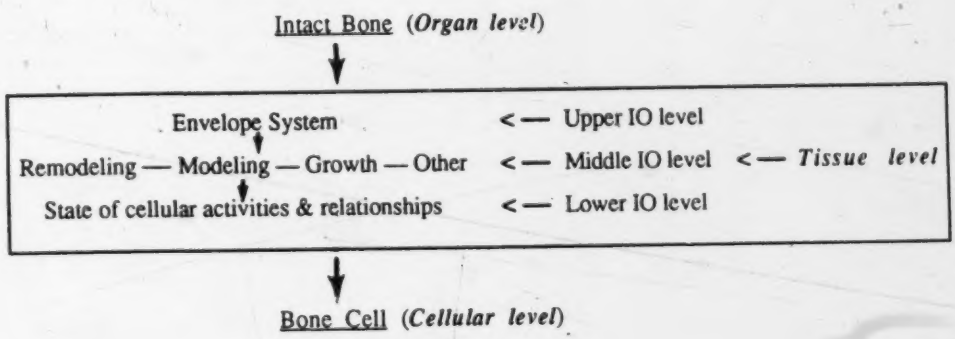
Scientists today have a better understanding of basic bone biology, and of advanced technologies for bone mass measurements and thus the direction for research becomes clearer, and hopefully, osteoporosis prevention and treatment will become a reality.

1.3 Bone Biology

Knowledge in the field of bone physiology has changed considerably with the "new bone" biology developed over the last 20 years. Thus many new concepts aimed at prevention and treatment of osteoporosis have been developed in recent times. Bone biology provides the basic understanding of the effects of various treatments on bone.

The fundamental principles of the new bone biology are covered in this section. How the bone responds to normal stresses and various pathological conditions will be discussed within specific sections (e.g. osteoporosis, exercise). Two distinct phases of skeletal development are delineated, they are modeling, the architectural design of the immature skeleton, and remodeling, the maintenance of the mature skeleton.

The conceptual framework of the new bone biology can be viewed as an organization ladder, with the lower rung being the cellular level, the middle rung the tissue level and the top rung the organ level.


Intact Bone (Organ level)
Envelope System
<— Upper IO level
Remodeling — Modeling — Growth — Other
<— Middle IO level
<— Tissue level
State of cellular activities & relationships
<— Lower IO level
Bone Cell (Cellular level)

Each level has its particular properties, and the bridging of the levels is referred to as the intermediary organization (IO), conceptualized by Harold Frost between 1963-66, but, not acknowledged or accepted by the scientific community until about 1980 (Frost, 1983). The IO encompasses the tissue level (the middle rung), but its role expands beyond this, since it bridges all the rungs of the ladder together (i.e. the cells to the organ

level) it basically controls the entire system. Researchers often do not look beyond the organ level to explain changes in bone mass with various interventions.

1.3.1 Bone Physiology

In general, the skeleton provides locomotion, mechanical strength and support to the body, and serves to protect vital organs. It also acts as a dynamic mineral reservoir of calcium and phosphate, yet it is not usually thought of as a highly metabolically active and extremely adaptable tissue.

As an organ, bone comprises both an organic (30%) and inorganic or mineral (70%) component. Collagen is the major component of the organic matrix, with noncollagenous proteins making up the difference, together they are referred to as osteoid. The mineral components, principally calcium and phosphorus, are known as hydroxyapatite. Other ions such as carbonate, magnesium, sodium and fluoride are also found in the mineral compartment.

Macroscopically two major types of bone are found in the skeleton — the cortical and trabecular bone. Structurally these bone types are distinct and occupy specific sites in the skeleton; their response to external factors such as calcium, exercise and estrogen are often different. Eighty percent of the skeleton, by mass, is cortical bone (also referred to as compact bone); this dense bone maintains cellular and nutritional communication through an interconnected canal-like network, called the Haversian system. Cortical bone is found mainly in the shafts of long bones. It is important to note that bone surface area:mass ratio for cortical bone is quite small. Trabecular bone, on the other hand, has a large surface area:mass ratio where mineral exchange is high. Thus, this bone is more responsive and metabolically active due to a high rate of mineral exchange compared to cortical bone. Only 20% of skeletal mass is composed of this porous trabecular bone (also referred to as spongy or cancellous bone), which architectually resembles a sponge.

Bone sites containing mostly trabecular bone are the distal and proximal parts of the long bones (e.g. radius, femur), the ribs and the vertebrae.

Metabolic activity takes place at four distinct surfaces. These surfaces are referred to as bone "envelopes" because each envelopes a characteristic volume of space. They are: (1) the periosteal surface; (2) haversian/canalicular surface; (3) the cortical-endosteal surface, and (4) the trabecular surface of the bone (Kaplan, 1987). Important metabolic exchange occurs mainly on the internal bone surfaces; the periosteal surface is relatively quiescent .

Bone can be thought of as existing in one of three states in the body. It can be fully mineralized bone which will be referred to as "old bone", it can be in the process of becoming mineralized, called the "mineralizing space" or it can be in a remodeling state, referred to as "remodeling space". Hypothetically, these states can be thought to exist as compartments, with the size of each dependent on an individual's genotype, physical status and lifestyle (Figure 1.2). Compartment size responds immediately to change. For example, upon immobilization many bone remodeling units (BRU's) are recruited simultaneously (referred to as "temporal coherence"), and would increase the size of the remodeling compartment. Temporal coherence occurs in response to metabolic changes within the body, and results in individual BRU's progressing, in step, at the same time through their usual sequence.

1.3.2 Bone Modeling

Bone modeling occurs only during skeletal growth. This is the only time in skeletal life where the bone envelopes move through space, resulting in changes in bone size and shape. Skeletal development starts in-utero, then after birth each stage of development (e.g. crawling, standing) and growth places various stresses and strains on the skeleton and over time the basic architecture of a functional and anatomically normal

adult skeleton is formed. Each developmental stage for the skeleton is essential for the next level to occur.

Figure 1.2 Hypothetical bone compartments that exist in the body

1.3.3 Bone Remodeling

Upon cessation of bone growth (i.e. epiphyseal closure) – at skeletal maturity – bone repair and replacement occurs through a "remodeling" process at the cellular level. Remodeling allows bone to adapt to the mechanical demands placed upon it and thereby maintains its mechanical competence and structural properties. Without this repair mechanism accumulation of microdamage within the bone, which occurs with normal everyday use, would quickly lead to bone fragility and eventual fracture.

Bone remodeling is dependent upon a sequence of discrete cellular events in bone called the bone remodeling unit (BRU). A completed remodeling sequence results in a new physical quantity of bone called the bone structural unit (BSU). A simple analogy gives a general insight into this complex bone remodeling process. Remodeling is similar to the laying down of bricks in a building; it is performed in temporally and spatialiy

discrete episodes with each brick representing a bone structural unit (BSU). If bone is viewed under a high powered microscope it gives the appearance of building bricks rather than a piece of poured concrete (Parfitt, 1981).

The metabolic activity of the skeleton is high; approximately 8-10% of total skeletal mass is resorbed and formed (turned-over) each year. This turnover rate implies that one new BSU is completed every 10 seconds throughout life (Parfitt, 1981). The average skeleton (70 kg man) contains about 1100 grams of calcium, resulting in a mean annual turnover of about 110 grams of calcium .

Two main types of bone cell are involved in the resorption and formation process; the osteoclasts and the osteoblasts, respectively. The osteoclast is a large multinucleated cell which migrates to newly exposed bone surfaces, and attaches to this surface with its ruffled membrane by resorbing collagen matrix (i.e. osteoid) using hydrolytic enzymes (e.g. acid phosphatase secretion). The osteoblasts then produce bone in the space excavated by the osteoclasts. The actions of these two bone cells are linked through a "coupling" mechanism which ensures that osteoblasts appear at sites excavated by osteoclasts.

The remodeling process can be generalized into three parts (Figure 1.3):

1. On a bone surface, the local remodeling cycle begins with "activation", a change in the local milieu that attracts bone remodeling units (BRU) — a co-ordinated sequence of cellular events — where osteoclasts resorb bone (1/10 mm^3) by release of hydrolytic enzymes over a 1 to 2 week period.

2. Once resorption is completed the osteoclasts disappear and lining cells deposit a cement substance — the reversal line.

3. Osteoblasts then appear and refill the cavity, first with a collagenous substance (i.e. osteoid), over about 3 to 4 months. Mineral is deposited in this osteoid matrix over several months beginning about two weeks after formation. Some of the osteoblasts become enclosed within the newly formed matrix forming the osteocytes.

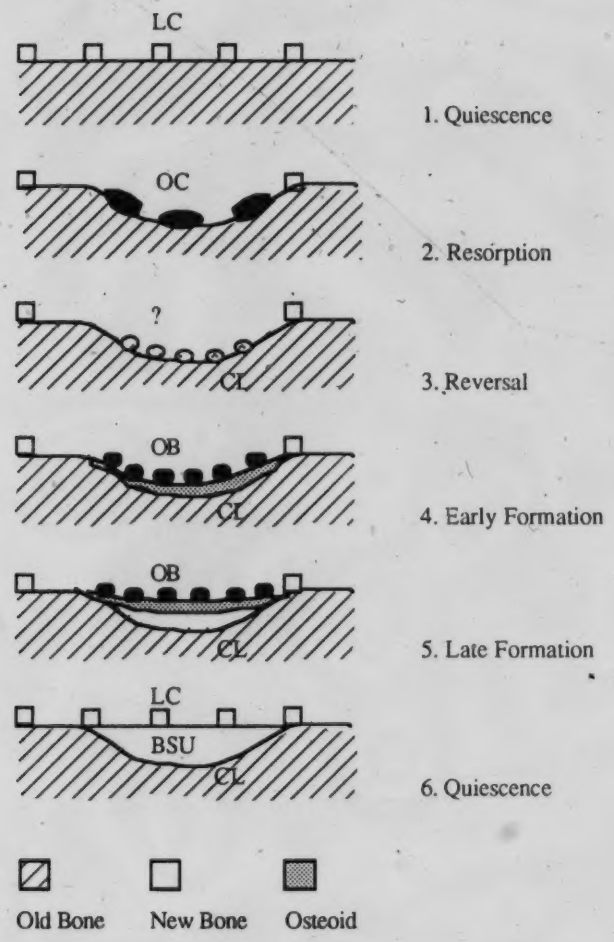


Figure 1.3 Normal bone remodeling of a single BRU and construction of a single new BSU

LC = flat lining cells, OC = osteoclasts, CL = cement line,
OB = osteoblasts, BRU = bone remodeling unit, BSU = bone structural unit

The time required for each BRU to complete its activities, from resorption to formation, is referred to as sigma (σ), and is about 3-4 months in cortical bone and 2-3 months on the trabecular bone surface in the young healthy skeleton (Parfitt, 1980). Mineralization, however, requires considerably greater time: about 80% complete at 2-3 months, but up to 2 years for 100% in the young healthy skeleton.

Experimental evidence indicates that activation occurs when remodeling stimuli (e.g. hormones, physical forces, microdamage) locally alter the behavior of dormant flat cells that line bone surfaces, thus exposing underlying bone surfaces that contain chemical attractants for the osteoclasts (Peck et al., 1987).

The control mechanism for remodeling is based on various systemic hormones and local factors. They can be classified as activators or inhibitors of bone remodeling and hence resorption. Putative activators include: parathyroid hormone; prostaglandins; vitamin D; thyroid hormone, and interleukin 1. Interferon, calcitonin, estrogens, and the diphosphonates are known to inhibit bone resorption. There is also evidence that mechanical strain in bone may change local surface electrical charge and thereby stimulate bone remodeling process.

Although bone turnover averages about 8-10% annually, this parameter varies greatly between individuals. Bone turnover depends upon both the "activation frequency", and the net bone balance in the BRU. The activation frequency is the number of BRU's that are initiated per unit time, and depends upon the status of the BRU precursor "pool" (i.e. the availability of BRU's to the demands of remodeling). In the human skeleton about 2×10^6 individual BRU's are active at any one time. When the BRU pool is filled — i.e. the activation frequency potential is at its highest — the number of active BRU's is usually low (about 5×10^5) resulting in a low turnover situation. When an activation occurs many BRU could be recruited simultaneously, and local bone density would be decreased as coherent resorption proceeds. When the BRU pool is depleted — i.e. there is low BRU activation potential — few BRU's are available for recruitment with activation. A high tissue level turnover (i.e. large numbers of active BRU's) and a large remodeling space (i.e. a transient bone deficit) are associated with this state.

This concept is easier to understand using immobilization (e.g. bed rest or casting) as an example. With immobilization there is a rapid and large increase in urinary calcium,

indicating bone resorption, which persists until a new equilibrium state is reached after about 90 to 180 days, at which time about 30% of the skeleton may be lost (approximately 500 g of calcium). With immobilization the remodeling compartment increases greatly in size, with a concomitant reduction in the volume of old bone (Figure 1.2). Increased bone turnover with immobilization is associated with other physiological changes: serum calcium increases, parathyroid hormone, Vitamin D3, and calcitonin decrease as does renal tubular reabsorption of calcium. All these changes lead to an increase in urinary calcium. With remobilization activation frequency is decreased to "pre-immobilization" levels. However, to replace the bone lost during a short (20 to 30 day) immobilization period may take up to 2 years in the young healthy skeleton.

This basic bone biology provides a general understanding of how various therapies to prevent bone loss will affect the skeleton. In the adult skeleton bone remodeling is influenced, among other agents by exercise, HRT and calcium.

1.4 Osteoporosis

Interest in osteoporosis heightened following a press conference held during the 1982 Annual Meeting of the American Society for Bone and Mineral research. At that time the impact of osteoporosis upon the aging population and society in general was widely publicized (Aloia, 1987). In 1984 the National Institutes of Health (NIH) sponsored a Consensus Conference on Osteoporosis the recommendations and conclusions of which were widely disseminated. In 1987 the NIH co-sponsored another conference on the research directions in osteoporosis.

This section briefly reviews risk factors, categories, clinical features, treatment, and prevention of osteoporosis.

Osteoporosis is often referred to as the "silent thief", as it slowly robs the skeleton of bone over time, weakening the skeleton to such a degree that normal everyday stresses result in fracture. The parts of the skeleton which sustain the most damage are those

containing larger proportions of trabecular bone, such as spine, ribs, and the ends of long bones (e.g. hip, radius). Primary osteoporosis is defined clinically only after a fracture has occurred.

1.4.1 Osteoporosis Risk Factors

Osteoporosis is a multifactorial disorder. A large number of risk factors (Table 1.1) have been established through epidemiological investigation. By finding commonalties between individuals who display symptoms and those who infrequently encounter the disease (e.g. Blacks) help to identify individuals at higher risk.

Table 1.1 Risk factors associated with primary osteoporosis

Factor	Increased Risk
Age:	advanced
Sex:	female
Race:	Caucasian or Asian
Habitus:	petite or thin fair skin, low body weight
Menopause:	natural, premature surgical
Family history:	positive history
Lifestyle:	sedentary excessive physical activity inadequate calcium intake cigarette smoking alcohol abuse

As bone loss occurs slowly, in both sexes, age becomes an important determinant of future bone density. Age and bone density are so closely related that if the age of a healthy women is known her bone density (lumbar spine & femoral neck) can be predicted within ±10% (Peck et al., 1987).

A low calcium intake throughout life may result in a lower peak bone mass and lower bone density many years later. Calcium absorption decreases with age, especially after age 70 years, which leads to a negative calcium balance. Five possible mechanisms have been suggested for this decreased calcium absorption: reduced vitamin D intake; decreased exposure to sunlight, and diminished efficiency of peripheral cutaneous conversion of vitamin D; impaired renal and hepatic conversion to the active form of vitamin D (1α, $25(OH)_2$ vitamin D) and increased intestinal resistance to vitamin D.

Menopause, whether natural or surgically induced (bilateral oophorectomy), accelerates bone loss in women as a result of an estrogen-deficiency. With exogenous estrogen replacement this accelerated bone loss can be prevented.

Hypogonadism has been reported in female long-distance runners, in women with anorexia-bulimia, and is associated with decreased vertebral density (Highet, 1989). Decreased gonadal function in men is also reported to have similar effects on bone mass (Peck et al., 1987).

The effects of various lifestyle factors on bone mass are cumulative. Low levels of physical activity, cigarette smoking, a high alcohol consumption, and weightlessness causes acute bone loss; physical stress increases bone mass.

Peak bone density is attained between about 28 to 35 years of age in most individuals. The risk of fracture later in life is strongly influenced by peak bone achieved during growth, and by the subsequent rate of bone loss. Peak bone density varies with sex and race, thus accounting for ethnic differences in the prevalence of osteoporosis. White women have the lightest skeletons and a greater incidence of osteoporosis, black women have heavier skeletons and low prevalence of osteoporosis. Racial differences in the incidence of osteoporosis may therefore primarily reflect differences in peak bone mass rather than in the rate of bone loss between various ethnic groups (Kaplan, 1987).

Cortical bone mass increases throughout adolescence reaching a peak level early in the third decade, shortly after the cessation of linear growth (Lane & Fries, 1988). At

approximately 50 years of age the bone shafts begin to thin; a process that continues for the rest of life (Mazess, 1982).

Generalized bone loss is more rapid in women for a few years after menopause with trabecular bone lost earlier than cortical bone (Mazess, 1982; Riggs, 1982). From about age 20 vertebral trabecular bone density in normal women decreases by about 1% per year; this loss rate increases to 2% to 5% per year in the early postmenopausal years (Riggs, 1982). Women lose approximately 35% of cortical bone and 50% of trabecular bone during their lifetime.

Osteoporotic fractures occur in those parts of the skeleton which contain proportionately larger amounts of trabecular bone (e.g. distal radius, vertebrae). Without trauma fractures do not occur, unless local bone density falls below a specific level, referred to as the "threshold level" which is about 1.0 g cm^{-2}, regardless of age or sex (Peck et al., 1987).

1.4.2 Categories of Osteoporosis

The osteoporoses can be divided into two major categories, primary and secondary (Peck et al., 1987). The classification of the condition is not universally accepted. Table 1.2 outlines the categories of osteoporosis and the subdivision within each category.

Postmenopausal and age-associated osteoporosis are the most common forms of this disease; they are classified as Type I and Type II osteoporosis, respectively (Table 1.3).

First described by Fuller Albright in the early 1940s, postmenopausal osteoporosis affects women during 15 to 20 years after ovarian failure (Peck et al., 1987). The principal clinical manifestations of postmenopausal osteoporosis are vertebral and wrist fractures (referred to as Colles' fracture). With the rapid loss of trabecular bone there is perforation of the plates and struts which characterize the local bone architecture,

Table 1.2 The Categories of Osteoporosis

PRIMARY OSTEOPOROSIS

Idiopathic
- juvenile
- premenopausal women
- middle-aged or young men

Involutional
- postmenopausal women (Type I)
- age-associated (Type II)

SECONDARY OSTEOPOROSIS (partial list)

Endocrine diseases
- hypogonadism
- ovarian agenesis

Gastrointestinal diseases
- severe malnutrition
- anorexia nervosa

Bone marrow disorders

Connective tissue diseases
- osteogenesis imperfecta

Miscellaneous causes
- immobilization
- chronic alcoholism

Table 1.3 Summary of Type I and II Osteoporosis

	TYPE I (postmenopausal)	TYPE II (age-associated)
Age (years)	55 - 75	> 70 (female) > 80 (male)
Ratio of females:males	6:1	2:1
Bone lost	mainly trabecular	trabecular & cortical
Rate of bone loss	rapid (short duration)	slow (long duration)
Fracture sites	vertebrae (crush) distal radius	vertebrae (multiple wedge) hip
Main cause	estrogen deficiency	age-related bone loss

which weakens the structure leading to collapse. Although all women lose ovarian function not all will develop osteoporosis. The development of osteoporosis is dependent on the rate of bone turnover: 25% of individuals have a high bone turnover, 45% are "normal", and 30% are low (Peck et al., 1987).

Age-associated osteoporosis (Type II), previously referred to as senile osteoporosis, occurs in both men and women. Loss of both cortical and trabecular bone over a lifetime results in bone mass values falling below the fracture threshold. Bone loss affects the entire aging population, however, those individuals with osteoporosis tend to have lower bone density than their healthy age and sex matched counterparts, and a rate of loss only slightly greater than their peers (Peck et al., 1987). A number of different fractures may occur, although hip and vertebral fractures are the most common. Multiple vertebral wedge fractures occur gradually, resulting in deformation, and dorsal kyphosis ("Dowager's hump").

Secondary osteoporosis is a consequence of another disease. Of the men and women who present with a spontaneous vertebral fracture, 40% and 20%, respectively, are a result of another disease such as gastrointestinal or endocrine disorders (Peck et al., 1987). The most common forms of secondary osteoporosis result from early oophorectomy; hypogonadism; subtotal gastrectomy; chronic obstructive pulmonary disease; immobilization, and pharmacologic doses of glucocorticoid or thyroid hormones (Peck et al., 1987).

1.4.3 Clinical Features

The most common clinical symptom of osteoporosis is back pain resulting from vertebral compression. This may arise spontaneously, but often occurs when some routine activity is performed, such as lifting a bag of groceries, or a child. When fractures first occur there are intermittent periods of acute pain followed by pain-free periods. With advanced osteoporosis a continuous dull, aching pain may develop from

the multiple vertebral compression fractures, and spinal deformity. In severe cases 10 to 20 cm of height are sometimes lost, with the rib cage eventually coming to rest on the iliac crest (Peck et al., 1987). In the active stage of osteoporosis it is not uncommon for one vertebrae to fracture every year. The back pain, loss of height, and spinal deformity are the most common symptoms clinically observed with osteoporosis.

No established methods to rebuild skeleton mass are available, however, sodium fluoride, diphosphonates, parathyroid hormone, anabolic steroids and vitamin D metabolites are presently under investigation (Peck et al., 1987).

1.4.4 Treatment & Prevention

Fluoride is incorporated into the hydroxyapatite crystals of the bone mineral, and significantly alters bone remodeling. It reduces bone resorption, increases bone formation, and directly increases osteoblastic activity (Peck et al., 1987). Fluoride has significant side effects, particularly gastrointestinal problems and while increasing trabecular bone mass may actually cause cortical thinning, and thus possibly increase susceptibility to fracture of the hip (Peck et al., 1987). One recently concluded major clinical trial of sodium fluoride found that sodium fluoride was no more effective than calcium carbonate in reducing vertebral fracture rate (Kleererkoper et al., 1989). If confirmed, these findings would preclude the use of sodium fluoride for the treatment of osteoporosis.

Calcitonin is known to inhibit bone resorption in osteoporotic subjects, however, it has not been shown to reduce fracture frequency (Peck et al., 1987). Calcitonin has been used in subjects who were not candidates for HRT, yet have osteoporosis or are at high risk. It is safe, has minor side effects, and its efficacy has been demonstrated. Previous use of calcitonin required parenteral administration, however, a nasal spray delivery system is now available although the agent is expensive.

The remaining treatment agents are still under basic clinical investigation, and insufficient data on safety and efficacy has been obtained for any conclusions to be drawn from their use.

The most important preventative strategy for osteoporosis appears to involve the attainment of a high peak bone mass. Starting with as much bone mass as genetically possibly provides the best protection against age-related bone loss. Leading a healthy lifestyle (i.e. regular physical activity, adequate calcium and good nutrition) both prior to and after skeletal maturity will help achieve peak bone mass as well as maintain it. Although more research needs to be done concerning preventative measures those presently being used include hormone replacement therapy, adequate calcium intake, weight-bearing exercise and calcitonin therapy .

Several theories exist which attempt to explain the etiology of osteoporosis at the tissue level. With age the life span of osteoblasts decreases and they are unable to complete their job which results in decreased bone production. The remodeling process is tightly coupled with osteoclasts removing bone and the osteoblasts filling these cavities. Normally the osteoclasts and osteoblasts work in conjunction; in osteoporosis this process is thought to go awry and osteoclasts remove the usual amount of bone but, the osteoblasts fail replace this loss. Alternatively, the osteoclasts excavate larger than normal cavities and the osteoblasts are unable to completely refill them.

1.5 *Bone Mass Measurements*

Bone mass measurements are used clinically to identify individuals at risk for osteoporosis through comparison with bone mass values in a healthy population, however, they are more commonly used in research settings to monitor the effects on bone of various experimental therapeutic regimens. This section reviews a number of the different types of technologies available. Since bone density is inversely related to the risk of fracture, early

identification and treatment of individuals with low bone mass may decrease or delay the incidence of fracture

Precision and accuracy, are primary considerations in bone mass measurement techniques. Precision is the reproducibility of the technique, accuracy the ability to measure the absolute amount of bone present. When repeated measures are made on a subject it is essential to measure the same site so observed changes are truly representative, and not a result of poor repositioning. In longitudinal studies good precision is necessary to monitor small changes over time. For example, in order to quantify a change of 4% in bone density (at the 95% confidence interval) the measurement should be made with a precision of better than 2%. The normal loss of bone is approximately 1% per year in premenopausal women, thus a long time observation would be needed before the results would be statistically significant. Thus techniques with measurement precision better then 1% are needed. The accuracy of a bone mass measurement technique (i.e. how close the measured value is to the true value) is critical in cross-sectional studies, and especially important for diagnostic purposes.

To summarize, the goals of methods for measuring bone mass are two fold: first, to detect small changes over time (precision), and secondly, to determine the absolute amount of bone mineral present (accuracy).

When choosing a technique to measure bone mass the type of bone (i.e. cortical or trabecular), and the measurement site (e.g. radius, vertebrae) are important considerations. Most metabolic bone diseases affect the trabecular bone to a greater extent than cortical bone due to the higher surface to volume (mass) ratio of trabecular, and thus it is usually necessary to distinguish between these bone types. Appendicular skeletal measurement sites (i.e. radius) are more commonly used than are axial sites primarily due to ease of measurement with good precision. However, since the axial skeleton has a higher proportion of trabecular bone than the appendicular skeleton it is more appropriate to measure the axial sites.

The available bone mass measurement methods are noninvasive [1] and quantitative, but they do not measure the "quality" of bone. Bone mass measurement techniques most commonly used in exercise-related studies will be reviewed: (1) single-photon absorptiometry (SPA), (2) dual-photon absorptiometry (DPA), (3) dual energy radiography, also known as dual energy x-ray absorptiometry (DER), (4) computed tomography (CT), and (5) in-vivo neutron activation analysis (IVNAA). Each method will be described briefly in terms of its technology, measurement site, accuracy, precision, advantages, and disadvantages. Table 1.4 summarizes the accuracy, precision, radiation dose, time per scan, and cost of these methods. It should be noted that the units of bone mass used by various methods differ thus making it difficult to compare results directly.

1.5.1 Single Photon Absorptiometry (SPA)

SPA was the first method developed specifically to measure bone mass in-vivo. (Cameron & Sorenson, 1963). Although the method has been greatly improved since that time the basic principle remains the same. SPA depends upon the attenuation of a beam of gamma ray photons (a unit of electromagnetic energy) by the bone. The gamma-rays are emitted from a point (1 mm diameter sphere) source of the radioactive isotope Iodine^{125} which is housed in a metal shield. This source shield has a shutter mechanism which allows a narrow beam of gamma-rays to emerge when opened. The photon beam is aligned with a collimated scintillation detector which records the number of photons which reach it. The object to be measured is placed between the source and the detector, and this fixed assembly translates across the bone producing a profile of photon transmission (and hence attentuation). The number of photons removed from the beam by the bone is proportional to the BMC of the object when appropriate correction for soft tissues is made (Cummings, 1987). The BMC is usually expressed as grams per centimeter (gm cm^{-1}).

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[1] very low dose ionizing radiation transmission measurements are generally considered as "non-invasive", but are invasive in the broadest interpretation, but without significant risk to the subject.

Table 1.4. Precision and accuracy of methods of bone mass measurements*

Method	Measurement site	Precision %	Accuracy %	Radiation Dose mSv	Time min
SPA	radius	2	<3	0.05	10
	os calcis	3	<3	0.05	10
DPA	total body	1	<3	0.01	60
	spine	2	<3	0.02	20
	femur	3	<3	0.02	20
DER	spine	1	<3	0.01	4
	femur	1	<3	0.01	3
CT					
special purpose	radius	<1	<3	0.1	10
commercial whole body					
single energy	vertebra	3-6	>15	>2.0	20
dual energy	vertebra	3-6	>15	>5.0	20
IVNAA	total body				
	hand	research procedure only		3 to 20	
	spine/trunk				

*References used to compile data in table: Barden & Mazess, 1989; Tothill, 1989.

The precision of SPA depends upon the bone site chosen (usually the radius), and upon repositioning in repeated measurements. For the distal radius reported precision varies from ±1.4% to ±7.6% (Hangartner, 1986). Accuracy is 5% to 6% and is influenced by the quantity of fat present, particularly in the bone marrow (Cameron et al., 1968). To compensate for variable soft tissue thickness a tissue equivalent cover is used to provide a constant thickness across the scan (either a water bath, water bag, or tissue-equivalent gel).

Advantage: This method is relatively simple to use, is low dose radiation, and is relatively inexpensive.

Disadvantage: Although SPA is widely used it has many shortcomings: (1) it is limited to the appendicular skeleton measurement (i.e. ulna, radius and os calcis) because of the requirement for constant thickness tissue around the bone (Wahner et al., 1984); (2) the appendicular sites do not appear to be as useful diagnostically as are the spine and femur; (3) the difficulty in repositioning the forearm, particularly the distal site, for repeated measures limits its precision, and hence usefulness in longitudinal studies; and (4) SPA lacks sensitivity for individual case diagnosis, as it measures total bone mass, (principally cortical bone); the sensitivity necessary to diagnose early osteopenia can only be achieved by measuring trabecular bone.

1.5.2 Dual Photon Absorptiometry (DPA)

The principle of DPA is similar to that of SPA but as the name suggests it uses a radioactive isotope source that produces photons at two energies. The photon beam emitted from the source has two principal energy levels (44 keV and 100 keV, using the radioisotope Gadolinium ^{153}, Gd^{153}). The use of transmission profiles at two photon energies in the analysis eliminates the need for constant thickness, and uniform soft tissue cover around the bone makes DPA more versatile than SPA. Bone "density" (g cm^{-2}, sometimes referred to as "areal density") is calculated by dividing the BMC (gram) by the area (cm^2) of the bone that is scanned.

The accuracy of DPA is better than three percent. However, since the fat content of the bone marrow is variable over time, inaccuracies still arise (Barden & Mazess, 1989). The precision of DPA has been reported as being between 1% to 2% for the lumbar spine (Barden & Mazess, 1989).

Advantage: DPA can measure BMD for the entire skeleton, as well as for important osteoporotic fracture sites, such as the hip and spine.

Disadvantage: Like SPA, DPA is not able to differentiate between trabecular and cortical bone. Further, in spine measurements the vertebral bodies cannot be separately measured from the spinous processes, osteophytes, and calcified plaques in the aorta (Cummings, 1987).

1.5.3 Dual Energy Radiography or Dual Energy X-ray Absorptiometry (DER)

DER is identical in principle to DPA, however, it uses an x-ray tube to generate photons at two energies, 40 and 70 keV. DER has good precision, which is site specific: 1% for the lumbar vertebrae, and 1.5% for the proximal femur.

Advantage: DER has several advantages over radioisotope-based DPA systems: (1) the spatial resolution is better due to higher beam intensity and better collimated beams; (2) scan time is reduced, and (3) the radiation dose is lower (Barden & Mazess, 1989).

Disadvantage: This technique still measures the total BMC (cortical and trabecular bone).

1.5.4 Computed Tomography (CT)

CT is an extension of SPA (Cann, 1988). A cross-sectional image of the bone is obtained by having the radiation source and the scintillation detector produce transmission profiles at many angular positions about the bone. From these multiple transmission profiles a two-dimensional image of radiation attenuation coefficients is reconstructed mathematically and displayed providing a cross-sectional "slice" of the bone. Usually

seven to ten contiguous "slices" are obtained at a particular site. A bone equivalent (such as K_2HPO_4) reference standard ("phantom") is required for calibration and the determination of BMD. Bone density is expressed as K_2HPO_4 equivalent (g). Using CT methods, cortical, trabecular or total BMD can be determined.

CT for bone density measures are of two types: (i) special-purpose CT systems used to measure the appendicular skeleton, and (ii) commercial whole-body CT systems used to measure the axial skeleton (Hangartner, 1986).

1.5.4.1 Special Purpose Computed Tomography

Special purpose CT has been developed for high-precision quantitative measurements of trabecular bone density in the peripheral skeleton, particularly the radius. In long-term clinical studies special purpose CT has a demonstrated precision (SD) of better than ±0.5% (Overton, 1987). The total of all systematic errors, which represents the accuracy of the method was found to be -0.6 to +3.4% (Hangartner et al., 1987).

Advantage: Special-purpose CT is a valuable research tool particularly for longitudinal studies. The ability to measure trabecular bone alone is a great advantage over other bone mass measurement techniques.

Disadvantage: Special purpose CT scanners are expensive to operate, available at only a few research centers in the world and are limited to appendicular sites.

1.5.4.2 Commercial Whole Body Computed Tomography

Cross-sectional images of selected vertebrae are generated using x-rays rather than γ-ray photons; both single and dual energy methods have been developed. The bone density is calculated by defining a region of interest (ROI) on the image generated and comparing its density to the that of standard phantom. The commercial whole body CT scanner requires that a calibration "phantom" is measured concurrently with the subject.

Advantage: The density of the trabecular core of the vertebrae or the whole vertebral body can be measured. When dual-energy CT is used this decreases the precision of measurement as compared to single-energy CT, but accuracy is improved.

Disadvantage: Although whole body CT are usually found in most large hospitals, they are usually difficult to access for bone research studies. Another limitation is the high radiation dose required to obtain bone mass measurements.

1.5.5 In-vivo Neutron Activation Analysis (IVNAA)

Using IVNAA, the entire body, or parts of the body, are irradiated with neutrons (neutral nuclear particle). Neutrons are generated using either a combination radioisotope source (Pu - Be), a nuclear reactor, or nuclear particle accelerator. When irradiated, stable calcium "48" (Ca^{48}) is converted to radioactive Ca^{49} which then decays with the emission of gamma-ray photons which are counted by scintillation detectors. Since 99% of body calcium is contained in the skeleton, the amount of Ca^{49} produced gives a good estimate of the amount of bone in the irradiated body part (Hangartner, 1986). The unit of measure is mass (g), which does not allow for comparison between individuals because it is influenced by the size of the skeleton, and therefore must be standardized by using various body measurements (Hangartner, 1986). Whole body scintillation counters are usually used to detect and count the γ-ray photon from Ca^{49}.

Depending on body size, the precision of IVNAA varies from ±2% to ±7% (Catto et al., 1973).

Advantage: IVNAA provides a reasonable estimate of total body calcium.

Disadvantage: A major disadvantage of IVNAA is the high radiation dose required to obtain measurements with good precision. Other limitations include: (1) low reproducibility (precision); (2) accuracy of the method can be poor in patients who have extraskeletal calcification (e.g. calcified aorta, etc); (4) use of a whole body radiation counter is required, and (5) IVNAA is only available at a few research centers.

1.5.6 *Safety*

Radiation doses for the different bone mass measurement methods are listed in Table 1.6. Radiation dose to the gonads is the critical parameter, SPA (radius), IVNAA (hand), CT (forearm) do not expose the gonads, and therefore a larger radiation exposure dose is allowed to those areas. A review by Kimmel (1984) provided radiation doses for the bone mass measurement techniques that follow. SPA involves only a 0.02 to 0.05 mSv dose to the radius, and since there is virtually no scatter, the gonad dose is negligible. Radiation exposure to the spine using DPA is 0.05 to 0.15 mSv, with a total dose to the ovaries of less than 0.02 mSv, and to the bone marrow dose less than 0.02 mSv. The dose in vertebral bone measurements using CT is significantly greater than SPA and DPA, at 2.0 to 2.5 mSv to the localized area, and a gonadal dose of less than 0.10 mSv. IVNAA requires even higher radiation doses, generally 2.0 to 5.0 mSv, however, partial body IVNAA requires proportionally less. To put these radiation dosages into perspective, a chest x-ray involves 0.20 to 0.40 mSv, and a lumbar spine x-ray up to 6.0 mSv.

Clinical bone mass measurements are not generally made on a routine basis. Many of the methods described here are used only for research because of the expertise required to perform some of the measures with good precision and accuracy, the capital cost, and measurement, and data evaluation times. More sophisticated methods of measuring bone are being developed which will have improved accuracy and precision and lower radiation dose. Hopefully these new and improved technologies will become available generally for the diagnosis and management of individuals with osteoporosis.

1.6 *Dietary Calcium Intake*

The role of calcium in the treatment and prevention of osteoporosis is controversial. Calcium deficiency undoubtedly can produce osteoporosis in growing experimental animals, however, in man this causal relationship is not proven (Nordin,

1960). The effects of calcium intake on bone mass have been studied using: epidemiological, bone mass measurement techniques, and metabolic balance studies. However, no firm conclusions concerning the long- or short-term effects of calcium have been established. It is difficult to consider the effects of calcium alone as it is involved in many nutrient and metabolic interactions, which in turn affect its absorption and utilization. Much controversy remains concerning calcium requirements for various age groups, and especially for postmenopausal women who have increased susceptibility to rapid bone loss. These issues, controversies and questions will be addressed in this section.

1.6.1 Epidemiology

Populations from the United States, Denmark, Central America, and Switzerland show no difference in bone mass despite the fact that they have significantly different calcium intakes (Kanis & Passmore, Part I, 1989). The emphasis placed on calcium intake for the prevention and treatment of osteoporosis is based on a general interpretation of epidemiology data; prevalence data for osteoporosis show that some geographic areas of low calcium intake also have the lowest incidence of osteoporosis (Chalmers & Ho, 1970). This places greater emphasis on the genetic and environmental influences on bone mass rather than on dietary calcium intake. One widely-cited epidemiological study (Matkovic et al., 1979) evaluated two Yugoslav populations. One district, Podravina, had an average daily calcium intake twice that (1014 mg) of the other district, Istra (481 mg). A life-long calcium intake was suggested by the authors to be an important determinant of bone mass in young adults, as a 50% lower incidence of proximal hip fractures existed in the high calcium district. However, a greater age-related bone loss was seen in the high-calcium district; and the lower fracture incidence thus appeared to be associated with a greater skeletal size at maturity rather than diminished bone loss in later life.

It is difficult to determine the effects of calcium on the skeleton from epidemiological evidence alone, as one cannot generalize from one population to another.

1.6.2 Calcium Effects Monitored through Bone Mass Measurements

Using various bone mass measurement techniques both cross-sectional and longitudinal studies have been performed to assess bone mass, and rate of bone mass loss at different sites in the skeleton. Through dietary calcium supplementation and subsequent monitoring of changes in bone mass it was thought that the effects of calcium on bone mass could be observed.

Longitudinal clinical trials, primarily in postmenopausal females, have shown that calcium supplementation in the range of 500 mg up to 2600 mg per day seem to have minor effects, if any, on the rate of bone loss measured by quantitative means (Recker et al., 1977; Nilas et al., 1984; Riggs et al., 1986; Riis et al., 1987). A study by Riis and colleagues (1987) monitored the effects of 2000 mg per day over 2 years in 15 healthy postmenopausal women, and 13 women who were on placebo. BMC was measured in the proximal and distal forearm by SPA and in the total body and spine (L2-L4) by DPA. Although these 2 groups decreased BMC significantly in all areas, the calcium-treated group showed a tendency toward a slowed loss of cortical bone in the proximal forearm and total skeleton. It should be noted that the daily calcium intake of the participants was not determined, and postmenopausal Danish women already have an average calcium intake of 1000 mg per day (Riis et al., 1987). Although this particular study found a "trend" towards slowed loss of cortical bone other studies, for longer periods of time (Riggs et al., 1986) and using larger doses of calcium (Recker et al., 1977), did not show any trends or significant changes upon supplementation to the diet. In the high risk areas, such as the spine there has been no change in the rate of bone loss with calcium supplementation (Riggs et al., 1986; Riis et al., 1987). One study monitored women in the age range of 23 to 88 years over approximately 4 years (Riggs et al., 1986). Half of

the women had a mean calcium intake of 497 mg per day and the other half 1422 mg per day over the study period. When adjustments were made for age, menopausal status, and serum level of estrogens, no relationship found between dietary calcium and the rate of change in BMD.

The studies discussed above, which used bone mass measurement techniques to monitor the effects of calcium supplementation (i.e. 500 to 2000 mg) on the rate of bone loss, have shown that calcium has little influence during periods of less than 4.5 years. Many factors must be considered with supplementation of calcium since the ability to absorb calcium decreases with age, and this varies greatly among individuals. The addition of calcium to the diet over a short period of time (i.e. 2 to 4 years) relative to the life span may have a small influence, but a high intake for longer periods of time may have a much more significant effect. It should be noted that most of the studies performed measured integral bone, and thus do not have the ability to monitor trabecular and cortical bone loss independently. Simply increasing calcium by dietary manipulation or through supplementation does not appear to prevent bone loss.

1.6.3 Metabolic Balance Studies

Calcium balance in osteoporotic patients was studied by Thalassinos et al. (1982) who found that a high calcium intake caused an increase in total calcium balance and net calcium absorption. In calcium balance studies Heaney et al. (1978) found that supplements of 1000 mg and 1500 mg of calcium per day were required to prevent negative calcium balance in estrogen-treated and untreated postmenopausal women, respectively. Balance studies are, however, very difficult to perform and variable results have been reported from different laboratories. Even with improved methods, many researchers are still skeptical of these types of studies. However, the NIH has based its recent calcium recommendation for women on balance studies despite the inherent limitations. Although difficult to conduct, calcium balance studies in humans have been

made for more than 30 years. Even at centers with good measurement technology balance studies provide variable results, and for this reason are interpreted with caution by contemporary researchers.

1.6.4 Calcium Requirements

It is known that calcium is essential for bone health, however, its role in the maintenance of bone mass in adult men and women is controversial and calcium intake recommendations throughout the world reflect this, with levels varying from 500 mg to 1500 mg per day (Shah & Belonje, 1988). It is often stated that an "adequate" intake of calcium is required to reduce "excessive" loss of bone tissue with advancing age, but the question remains as to what is considered "adequate".

Over 40% of postmenopausal women in Canada have calcium intakes lower than the Recommended Nutrients Intakes for Canadians (RNI) of 800 mg per day (Shah & Belonje, 1988). In 1984 the NIH Consensus Development Conference for the prevention of fractures in Osteoporosis recommended 1000 mg per day for premenopausal women and postmenopausal women treated with hormone replacement therapy, and 1500 mg per day for untreated postmenopausal women (NIH, 1984). Much criticism has been drawn to these recommendations since the average calcium intake of women in the USA is only 500 mg per day, making it is impractical for women to achieve 1000 to 1500 mg per day through diet alone (the equivalent of 5 glasses of milk). This places most women in a situation of life-long commitment to calcium supplementation or living a so-called "inadequate" intake.

Calcium intake prior to skeletal maturity appears to be important for attaining peak bone mass, however, increasing calcium intake above the RNI after menopause appears to have little effect on the rate of loss of bone mass.

Dawson-Hughes et al. (1987) suggested a threshold of calcium intake below which increased calcium in the diet is likely to be beneficial in reducing mineral loss in the

spine. Postmenopausal women who ingested less than 405 mg of calcium per day appeared to lose bone more rapidly than those whose intake exceeded 777 mg per day. The calcium intake was based on the sum of dietary and supplemental sources. However, the value of an increased calcium intake has yet to be demonstrated in postmenopausal women.

Some women lose bone mass at a much faster rate around the time of menopause despite dietary calcium intake remaining relatively constant. There is a concomitant increase in urinary calcium excretion and reduced intestinal absorption at this time (Kanis & Passmore, Part II, 1989). Is this decrease from intestinal calcium absorption a cause or consequence of osteoporosis? Similar to immobilization and weightlessness there is also increased urinary calcium excretion at menopause and subsequent bone mineral loss regardless of the level of calcium supplementation.

There is no evidence that calcium increases bone mass after skeletal maturity, and inconclusive findings with respect to calcium influences on age-related bone loss (Kanis & Passmore, Part II, 1989). A general consensus is that calcium alone should not be used as a form of therapy for osteoporosis, but should be used as an adjunct to other treatment regimes.

There are many complex interactions of calcium in the calcium regulatory mechanism. Calcium can influence vitamin D metabolism such that it decreases total cellular activity of the bone involving both osteoblasts and osteoclasts, thus calcium is considered a depressor of bone remodeling.

1.7 Hormone Replacement Therapy

Fifty years ago, Fuller Albright found that postmenopausal women most frequently presented with osteoporosis. From this observation and other clinical data Albright hypothesized that an estrogen deficiency was responsible for the observed bone loss (Albright et al., 1941). It was not until the early 1960s, however, that the causal

relationship between ovarian failure and osteoporosis was confirmed through prospective clinical studies using techniques that allowed accurate and reproducible measurement of bone mass by noninvasive methods (Lindsay, 1987). However, it was not until the mid-sixties that the use of estrogen replacement therapy for postmenopausal osteoporosis was considered (Lindsay, 1982), and results from some of these early studies were not published until 1976 (Lindsay, 1982).

To date no treatment exists that can produce sustained increases in bone mass in the depleted skeleton. The clinical emphasis is therefore placed on methods to prevent bone mass loss in the early menopause and to reduce rate of bone loss in established disease. Based upon the accumulated experimental evidence estrogen replacement is the most effective therapy for reducing bone resorption, and thus for preventing osteoporotic fractures later in life. In most clinical applications estrogen is now used in combination with a progestogen so the treatment is referred to as hormone replacement therapy (HRT).

The hormonal changes occurring at menopause, the evidence that supports the association between estrogen deficiency and bone loss, the efficacy of HRT and recommendations for use, including: dose; route of administration; duration of use and recipients; risks versus benefits, and mechanisms of action are all discussed in this section.

The clinical use of HRT is primarily in the treatment of clinical symptoms associated with the menopause, however, it is also used as a prophylaxis against cardiovascular diseases and osteoporosis.

1.7.1 Hormonal Changes

Ninety percent of postmenopausal women have low circulating levels of estrogen (Scott & Cumming, 1985). Prior to ovarian failure the major circulating estrogen is estradiol, after ovarian failure estrone becomes the major steroid. Although estrone levels are higher both estrone and estradiol are greatly reduced relative to levels in young

women. For example, premenopausal women produce 80 to 300 µg/day of estrone, and 80 to 500 µg/day of estradiol, while postmenopausal produce only 40 µg of estrone, and 6 µg estradiol (Scott & Cumming, 1985). In postmenopausal women the ovaries and adrenals contribute very little to serum estrogen levels which depend mainly on peripheral fat conversion of the estrogen precursor, androstenedione (Scott & Cumming, 1985). Excess body fat appears to be related to higher estrogen levels, although this finding is controversial (Scott & Cumming, 1985).

1.7.2 Estrogen Deficiency and Bone Loss

Providing women with HRT when estrogen deficiency occurs decreases the likelihood of future osteoporotic fracture. Reduction of endogenous estrogen levels occur at natural menopause, after premenopausal bilateral oophorectomy, in cases of amenorrhea (e.g. athletic amenorrhea), and all these conditions are all associated with decreased bone mass.

The most convincing evidence to support the relationship between estrogen deficiency and loss of bone mass is in studies involving cyclic women who underwent bilateral oophorectomy (Barzel, 1988). With immediate cessation of estrogen production rapid loss of both cortical and trabecular bone was observed. Trabecular bone loss in the spine has been documented at up to 8% per year after oophorectomy (Ettinger, 1987), and estrogen replacement therapy after oophorectomy prevents accelerated bone loss (Ettinger et al., 1987).

At natural menopause the changes in serum estrogen levels are not as abrupt as with oophorectomy, and the initial loss of bone mass is gradual. Even though an estrogen deficiency is maintained from the time of menopause throughout a woman's life, the rate of bone loss does not remain constant. There is a predictable bone loss pattern with estrogen deficiency, regardless of etiology. Initially, an annual loss of 5-8% of trabecular bone is seen; cortical bone decreases by 1-3% annually. After 10 to 15 years

the annual rate of bone loss decreases at which time about one-third to one-half of the skeleton may already be lost causing skeletal fragility with vertebral collapse, and minimal trauma fractures in the distal radius. After another 10 to 15 years of slower bone loss hip fractures begin to occur more frequently as cortical bone losses become important (Ettinger, 1988).

1.7.3 Efficacy of HRT

There is strong evidence from several well-controlled studies confirming that HRT prevents bone loss in estrogen deficient women. There is also some opportunity to recoup lost bone mass if HRT is started early, however, if treatment is delayed for several years the ability to rebuild bone is lost, but further loss of bone is reduced (Lindsay, 1987). Women treated with estrogen soon after the onset of the menopause have a lower prevalence of osteoporotic fractures than untreated women (Ettinger et al., 1987; Ettinger, 1988; Ettinger 1986).

Christiansen et al. (1981) have clearly demonstrated the efficacy of HRT. Using a crossover design they were able to show that the effects of HRT could be turned off and on. With HRT treatment forearm BMC actually increased (3.7%), but decreased (5.7%) in the placebo group over the 3 year duration of the study. When the HRT was discontinued, however, the rate of bone loss was identical to that for the placebo group.

Lindsay (1989) demonstrated that estrogen treatment of postmenopausal women prevents peripheral cortical bone loss for as long as estrogens are given (10-12 years), and that bone loss begins again when therapy is withdrawn. After 10 years of therapy the axial bone mass measured by DPA is some 25% greater in estrogen treated women than in an untreated population, and femoral neck bone mineral is 12% greater (Lindsay, 1989).

Calcium supplementation to raise the total dietary calcium intake to approximately 1500 mg has been found to have a protective effect on bone mass when used in conjunction with HRT. Calcium appears to operate synergistically with estrogen, to the

extent that estrogen dosage can be reduced by half and still retain its effectiveness in preventing bone loss (Ettinger et al., 1987).

Cauley et al. (1988) studied the effects on cortical bone of interactions between hormone levels and lifetime calcium intake in 174 postmenopausal women, and the combination revealed an additive relationship. Women with high estrone levels and high calcium intakes had significantly higher bone density than women with less calcium and/or estrone.

The effects of progestogens alone on bone mass is less clear at this time, although studies are ongoing. Preliminary result have indicated that they offer little or no protection against spinal mineral loss after menopause (Ettinger, 1988).

1.7.4 Dosage

Conjugated equine estrogens (Premarin™) is the preparation most frequently used for therapy of menopausal symptoms (Scott & Cumming, 1985). Many factors other than dosage influence the effectiveness of the estrogens for menopausal symptomology, for example the type of hormone used, route of administration, the rate of absorption, and the addition of calcium.

To prevent bone loss and relieve symptoms at menopause the minimal effective dosage for estrogen has been found to be 0.625 mg of conjugated estrogens or its equivalent (i.e. 1 mg of micronized estradiol, 1.25 mg of piperazine estrone sulfate and 0.05 mg of transdermal estradiol, 2 mg 17β-estradiol, and 25 μg ethinyloestradiol) (Conference Report, 1987; Ettinger, 1989). This estrogen dose has also been shown to have a beneficial effect on lipoproteins, and when coupled with a daily calcium intake of at least 1500 mg, these estrogen dosages can be reduced by half (i.e. 0.3 mg conjugated estrogens) and still be effective (Ettinger et al., 1987; Ettinger, 1988). Using lower estrogen dosages is beneficial since less endometrial stimulation occurs, and thus a lower

frequency of withdrawal bleeding and fewer gynecologic complications occur (Ettinger, et al. 1987).

The addition of a progestogen to HRT is basically to protect the endometrium from hyperplasia and cancerous changes, and is necessary only in women who have an intact uterus. Cyclic therapy is most commonly prescribed, where progestogens are given for 10 or more days in each estrogen cycle, and has proven effective. A study recently published by Riis et al. (1988) demonstrated that a "continuous" estrogen-progestogen treatment in postmenopausal women over a 2-year period is also effective prophylaxis against bone loss. Low-dose progestogen taken continuously with oral estrogen resulted in decreased bleeding with length of therapy, and a higher incidence of amenorrhea with an atrophic endometrium (Weinstein, 1987).

1.7.5 Route of Administration

Parenteral (transdermal patch) and oral (pill) delivery of estrogen and progestogens have their advantages and disadvantages. Transdermal estrogen recently became available for the treatment of menopausal symptoms, and additional investigations must be done to confirm its efficacy in the prevention of osteoporosis.

Estradiol produced by the ovaries goes directly into the systemic circulation. Oral estrogens, however, must first pass through the intestines then into the portal circulation and through the liver (which is responsible for considerable metabolic degradation). The quantity of oral estrogens reaching the general circulation is much lower than that reaching the liver. The liver metabolism of estradiol is referred to as "first-pass metabolism" (Judd et al., 1983). Parenteral estrogens, however, avoid the first pass through the liver, therefore the dose can be considerably smaller. With transdermal estradiol a dose of 50 µg transdermal dosage is considered equivalent to a 0.625 mg oral dosage.

There is no data on the interaction between exercise and estrogen. Some forms of exercise may have additive effects similar to calcium, or result in increased sensitivity to

estrogen, similar to the effects of exercise on insulin sensitivity. However, it is established that the effects of estrogen are dominant over the effects of exercise in amenorrheic athletes.

1.7.6 Duration of HRT

Studies which have demonstrated beneficial effects of HRT on the skeleton were initiated within three, and sometimes up to five years after menopause (Barzel, 1988).

Once a significant amount of bone is lost HRT is unable to replace this but it does slow the rate of loss. Intervention starting 15 to 20 years after menopause is not useful at that time since bone loss may have slowed down significantly, and also the side effects of HRT would be even more undesirable (i.e. withdrawal bleeding). There are no set guidelines for the duration of HRT therapy, however, Collins (1988) recommends it should continue to age 70 years, and the Consensus development conference for prophylaxis and treatment of osteoporosis recommends at least 10 years (Conference Report, 1987).

1.7.7 Recipients of HRT

Women "at risk" for developing osteoporosis should be prescribed HRT (Conference Report, 1987). Although this statement appears straightforward it is ambiguous. There is presently no means of identifying women who will eventually become osteoporotic, or if HRT would be effective within this subpopulation to prevent osteoporosis. No prospective study has yet chosen subjects on the basis of risk factors associated with osteoporosis (i.e. fair skin, low body weight, smoking, etc) and determined the efficacy of HRT. White postmenopausal women are most commonly involved in studies on HRT and bone mass. HRT does not preferentially protect individuals who have various risk factors, its effects appear to be universal, and to date no retrospective, epidemiologic studies have demonstrated any interaction (Barzel, 1988).

1.7.8 Risks versus Benefit

The risks and benefits for HRT (i.e. estrogen alone, and in combination with progestogen) must be considered for each woman. Not only should the medical risks (i.e. endometrial cancer) be considered but also personal and emotional issues (i.e. "taking a pill everyday", withdrawal bleeding) which influence compliance.

Positive effects of estrogens include: amelioration of menopausal symptoms, maintenance of bone integrity, and prevention of heart disease and stroke. Negative effects include: possible causal agent for endometrial and breast cancers, and an increase in biliary disease (Mack & Ross, 1989)

It is well established that HRT eliminates menopausal symptoms (hot flushes, episodic sweating, vaginal dryness, urethral irritation), and can reduce the rate of bone loss. It has also been demonstrated that dietary calcium utilization is improved by estrogen (Lindsay, 1987).

An increased risk of developing endometrial carcinoma has been clearly documented in patients receiving postmenopausal estrogen replacement (Shapiro et al., 1980), and is dose related. However, risk is substantially reduced with the addition of a progestin for at least 10 days of each estrogen cycle. The incidence of breast cancer has not been found to increase with postmenopausal use of estrogen (Kaufman et al., 1984; Gambrell et al., 1983), but this issue remains controversial (Mack & Ross, 1989).

Controversy also exists concerning the addition of progestogens to the therapy (Mack & Ross, 1989). There is concern about breast cancer, heart disease, stroke and the magnitude of the expected reduction in endometrial cancer. At this time there is relatively little empirical information about the use of estrogens supplemented with progestogens, and this must be studied further. Weinstein (1987) found that when medroxyprogesterone acetate (2.5 mg) was used continuously with estrogen there was no

detrimental effects on serum lipoprotein levels (i.e. cholesterol, LDL, HDL, VLDL and triglycerides).

On the emotional side, it has been found that most women do not want to take hormones (Notelovitz, 1989). Their concerns stem from, not wanting to put "foreign substances" into their body, to the possible side effects, and the resumption of menstruation.

In women with an intact uterus, one of the least acceptable consequences of combination HRT is withdrawal bleeding, as well as the need for endometrial biopsy (Notelovitz, 1989). However, there are ways to reduce withdrawal bleeding by continuous combined therapy (Notelovitz, 1989). This approach has been studied for its efficacy and safety (Weinstein, 1987).

1.7.9 Mechanisms of Action

Although the mechanisms of estrogen effects on bone are not known, the recent identification of estrogen receptors in osteoblast-like cells (cultured human bone cells) indicates that there is a direct mode of action on the skeleton. The first data on estrogen receptors was published in 1988 (Komm et al., 1988), and suggested that estrogen action on bone is through a classical estrogen receptor-mediated mechanism, allowing control over the extracellular matrix and other proteins involved in the maintenance of skeletal mineralization and remodeling. The target cells (osteoblast-like) display a steroid-specific, saturable, and temperature-dependent response to estrogen treatment (Eriksen et al., 1988). Kaplan et al. (1988) was the first to identify both estrogen and progesterone receptors directly from human bone cell samples.

1.8 Exercise

Exercise, in general, is thought to be beneficial for the skeleton. The specific type, intensity, and duration of exercise and its effectiveness in preventing accelerated

bone loss is not known. Although results from studies on immobilization in animals and humans, and exercise in animals and athletes have provided valuable information concerning physical activity levels and bone mass, the data is not adequate to develop an exercise prescription for increasing or maintaining bone mass. Postmenopausal women are of particular concern — and the potential effects exercise may have on the skeleton. At this time only general recommendations are given to such women concerned about maintaining their bone mass. For example, women are often encouraged to keep-up a "reasonable level" of physical activity throughout life (Lindberg et al., 1987). Also, the NIH Consensus Conference on Osteoporosis (1984) recommendations for exercise are vague: "Modest weight-bearing exercise, such as walking, is recommended". These general exercise recommendations result from the lack of sufficient experimental evidence concerning exercise effects.

In the past animal studies have been the focus of attention for monitoring the effects of exercise on the skeleton, particularly because bone mass and muscle mass could be directly determined upon sacrifice. However, clinical research in the area of bone response to exercise has had a tremendous growth over the past 10 years, due partially to improved technology for bone mass measurements in humans, but primarily from the need to prevent and treat osteoporosis.

This section reviews published data on the skeletal effects of various forms of mechanical usage (e.g. immobilization, exercise) specifically considering, immobilization; animal research; bone mass and its relationship to muscle mass and strength; elite athletes and the effects of excessive training. Finally, the area of specific interest, that is the effect of exercise intervention in normal female populations and the underlying mechanism hypothesized to influence bone mass will be discussed.

1.8.1 Immobilization

The effects of immobilization on calcium metabolism have been recognized for many years (Deitrick et al., 1948; Whedon et al., 1949). Two areas of particular public interest and concern stimulated research concerning bone mass and immobilization. These were: the epidemic of poliomyelitis in the early fifties, and subsequent care of paraplegic patients, and the entry of man into the weightless environment of space (Schoutens et al., 1989). In each of these situations stress was removed from bone, and the resulting effects on bone mass provide important insights into the effect of physical activity on bone.

Increases in urinary calcium excretion were first observed in the cosmonauts on board Vostok 2 and 3 suggesting bone loss, however, bone mass in astronauts was not measured directly until 1964 and 1965 (Gemini space missions IV, V, VII), when radiographic densiotometry became available (Rambaut & Goode, 1985). In general, astronauts subjected to an effectively weightless environment have shown losses of about 4% per month for trabecular bone and 1% for cortical bone (Mazess &Whedon, 1983). The bones most affected during weightlessness are those that usually bear weight; the upper limbs appear to be more resistant to loss (Rambaut & Goode, 1985).

Rates of bone loss similar to those seen in astronauts during flight have been reported in patients with casting after sports injuries, bedrest, and with immobilization due to paraplegia and poliomyelitis (Andersson & Nilsson, 1979; Mazess & Whedon, 1983; Abramson & Delagi, 1961). In young persons bone loss is reversible upon remobilization providing the duration of immobilization is less than 4 to 6 months; restoration of bone mass, however, is considerably slower than bone loss, and may be incomplete in some individuals (Mazess & Whedon, 1983). Trabecular bone loss from immobilization is mainly from trabecular thinning, which is reversible upon remobilization, however, when a trabecular plate or rod is completely resorbed it cannot

be restored. The degree of trabecular resorption depends primarily on the length of immobilization, but other factors also influence bone loss (i.e. age, sex, general health, etc.)

Study of osteopenic patients with polio, muscle function has proved important for bone health. Even though weight-bearing activities were performed by such patients no decrease in hypercalciuria resulted (Dalsky, 1987). These findings suggest that weight-bearing alone is inadequate for bone mass maintenance; muscular contractions are also needed in association with weight-bearing.

Over a 25-week period, after initial spinal cord injury, patients showed a 33% reduction in trabecular bone volume of the iliac crest (Mazess & Whedon, 1983). The calcium losses observed in these patients was higher than in otherwise healthy volunteer bedrest subjects, yet patients with complete spinal cord lesions had higher calcium losses than those with incomplete lesions (Mazess & Whedon, 1983).

Abramson and Delagi (1961) stated that "muscle action is the most effective stress upon bone preventing disuse osteoporosis", and that "weight-bearing is much less effective than muscle action but it is probably not entirely ineffective in limiting osteoporosis".

The intensity and duration of muscular activity may be important, as well patient positioning seems to be a critical factor (e.g. an upright posture) (Issekutz et al., 1966).

A few mechanisms have been proposed for bone loss during immobilization, one is a decreased level of osteoblastic activity (Nordin, 1960). The increase in urinary calcium excretion which occurs with immobilization suggests destruction of the bone tissue, rather than impaired formation (Nordin, 1960). Another hypothesis is that absence of pressure forces on the skeleton are primarily responsible for disuse osteopenia (Sinaki, 1989). This may be the result of piezoelectric forces within the bone generated through deformation of crystalline hydroxyapatite.

From studies using various forms of immobilization it is evident that muscular contractions, gravitational and mechanical forces must be present to maintain bone mass, however, other physiological and metabolic parameters also affect the skeleton (e.g. changes in circulation may influence bone loss). Much is learned from studies involving immobilization and bone mass. First, that weight-bearing activity is required to maintain bone mass particularly in weight-bearing bones; second, a negative calcium balance results from the absence of muscular activity, while muscular activity must be present for exercise to be effective in maintenance of bone mass; and third, trabecular bone is more sensitive to immobilization than cortical bone, and furthermore, trabecular bone loss may be permanent.

1.8.2 Animal Studies

Animal studies have clearly demonstrated an increase in bone volume and BMC in response to exercise (Schoutens et al., 1989). Rats, mice, rabbits, dogs and swine have been exercised and increases observed in bone density, cortical thickness and/or cross-sectional area (Smith & Gilligan, 1987).

Of particular interest are the studies performed by Lanyon et al. (Lanyon, 1984; Lanyon et al., 1986; Rubin & Lanyon, 1987). In one study a turkey hen wing (ulna) model was used, the relationship between strain variation and subsequent bone remodeling activity was measured. Strain gauges were attached to selected sites on the bone surface to measure strains induced by external loads. Changes in the mechanical strain environment in bone were found to be a principal determinant of its remodeling. Remodeling, based on mechanical usage, was found to be dependent on four principal factors; the number of strain cycles; peak strain magnitude; rate of strain change and strain distribution (Lanyon, 1984). Two of the four principals outlined are similar to those used in weight-training to increase muscle mass in humans, i.e. number of repetitions and sets (strain cycles), and the amount of weight lifted (strain magnitude).

A constant compressive (static or isometric) load does not appear to increase bone mass, while dynamic loading does, even with the same load used in the static situation (Lanyon, 1984). Although other factors are important, the number of loading cycles showed the most striking effects on bone remodeling (Lanyon, 1984). The ulna, in vivo, was subjected to 0, 4, 36, 360 or 1800 consecutive loading cycles per day over a 6 week period. At 4 loading cycles per day bone resorption was prevented; with 36 cycles BMC increased by 33%, while at 360 and 1800 cycles BMC did not increase above the level seen at 36 cycles.

Strain in bone is measured in units of microstrain (μE). A peak strain magnitude of 500 microstrains was insufficient to prevent bone loss, while at 1000 μE bone area was maintained, and strains above 1000 μE resulted in new bone formation.

In a sheep model strain distribution was measured in the radius during locomotion after removal of the ulna. The change in strain distribution in the radius to compensate for the structural loss of the ulna had a large influence on the development of that bone.

How these strain application factors in animals can be applied to human exercise prescription to build or maintain bone mass is still unknown. This animal research, however, provides guidelines for the design of future human exercise studies. If the animal results are applicable to humans then there are important implications for the treatment of individuals at risk for osteoporosis.

1.8.3 Bone, Muscle and Strength

"Robust femurs do not support weak thigh muscles, nor do slender femurs support massive muscles", thus implying a relationship between the strength and stiffness of bone and the strength of its associated muscles (Frost, 1988). These observations have been voiced since the early 1900s yet the true nature of the relationship is obscure as conflicting data exists on the relationship between muscle strength and bone mass (Frost, 1988).

Both muscle mass and muscle strength have been studied in relation to bone mass. Animal studies have shown that with exercise, muscle mass and bone hypertrophy together (Saville and Smith, 1966; Saville & White, 1969). Doyle et al. (1970) studied the relationship between muscle mass and bone mass in humans. They found that the weight of the left psoas muscle was significantly related to the ash weight of the third lumbar vertebra (autopsy). Both bone mass and muscle mass decrease with increasing age. The effect of age, however, disappears in both men and premenopausal women when BMC is divided by the muscle mass. With postmenopausal women the loss of bone is still apparent even after the muscle mass correction is made (Schoutens et al., 1989).

The relationship between muscle strength and BMC was not studied in humans prior to the 1970s mainly due to the lack of in-vivo methods to measure BMC. Like muscle, bone is affected locally by mechanical forces; the response generally occurs in the area where strain is increased. Although muscles respond to dynamic (isotonic) and isometric exercise, bone hypertrophy apparently occurs only with dynamic strain.

Weight lifters and body builders already apply the principle of high intensity (or load) with low repetition to maximize muscle hypertrophy. A study performed by Nilsson and colleagues (1978) compared BMC in 24 male weight lifters and 21 professional ballet dancers to age-matched controls. The results indicated that the BMC was higher in both dancers and weight lifters compared to controls.

Dalsky et al. (1989) reported preliminary results predicting BMD from muscular strength and fat free mass in 10 male runners and 6 power lifters. Aerobic power did not significantly predict bone density at any site. They concluded axial and total body BMD can be predicted more accurately from fat free mass and muscular strength than aerobic power or BMI in trained men.

In a group of top ranked athletes the greater the lower limb exertion required from the athlete's sport the greater the femoral bone density (Nilsson & Westlin, 1971).

However, no relationship was found between quadriceps force and bone density in the distal femur.

Granhed et al. (1987) found that BMC in the lumbar spine of world-class power lifters would increase in response to the load lifted (annual load of greater than 1000 tons), and that BMC was closely related to the annual training dosage.

To eliminate the bias of athletic body types normal subjects must be used to test muscular strength rather than athletes. Sinaki et al. (1974) found that the decrease in BMC in the radius of women was not related to the loss of muscle strength in the arms (elbow flexors and power grip). BMC of the radius decreased with age in women but not men, however no significant correlation exists between strength and BMC with increasing age. Sinaki & Offord (1988) studied the effect of back muscle strength on BMD of the spine (L2 through L4) in 68 healthy postmenopausal women. There was a significant, but low, positive correlation ($r=0.34$, $p<0.005$) between BMD and back extensor strength, suggesting that back muscle strength may contribute to the BMD of vertebral bodies. Colletti et al. (1989) demonstrated that muscle-building exercise is associated with increases in BMD at weight-bearing sites (i.e. spine, femur) but not nonweight-bearing sites (i.e. radius cortical bone) in 12 men who had regularly weight-trained for an average of 6 years.

Three recent studies have looked at the effects of muscle strength on bone mass (Pocock et al., 1989; Bevier et al., 1989; Judge et al., 1989). Pocock et al. (1989) reported that muscle strength, as measured using Cybex II on the knee extensors and the elbow flexors, was found to be an independent predictor of BMD at the proximal femur, lumbar spine (L2-L4) and forearm in 73 healthy females (age 20 - 75 years). Bicep strength was a better predictor of both upper and lower limb bone mass than quadriceps strength, suggesting it is a reasonable indicator of overall muscle strength. Bevier et al. (1989) also reported the effect of muscle strength on BMD in 91 older healthy men and women (age 61 - 84 years). In women, grip strength correlated with forearm bone

density ($r=0.37$, $p<0.05$) and spine density ($r=0.28$, $p<0.05$). In men, grip strength correlated with forearm density ($r=0.47$, $p<0.05$) and back strength was significantly correlated with both spine ($r=0.46$, $p<0.01$) and forearm ($r=0.46$, $p<0.01$). Judge et al. (1989) found that lower extremity strength, tested by 1 RM on a Cybex Eagle knee extension machine and a Keiser leg press, was an independent predictor of BMD in older women (average age of 67.1 years). Fitness estimated by treadmill time using a modified Balke protocol was not correlated with bone density of the femoral neck or the trochanter.

Although muscle strength is easier to measure it yields a weaker correlation than directly measuring muscle mass. In women, weight-bearing bones appear to be related to muscle strength, however, non-weight-bearing bones (i.e. radius) have a weak correlation or none at all. Sandler (1988) suggests that normative data for muscle strength be used as a standard for mechanical loading of the skeleton, since this may represent the amount of bone mass present and help to inexpensively identify individuals at risk.

1.8.4 Athletes

Several cross-sectional studies have shown that athletes have greater bone mass than age-matched sedentary controls (Dalen & Olsson, 1974; Nilsson & Westlin, 1971; Aloia et al., 1978; Huddleston et al., 1980). In descending order of bone mass, a significant difference has also been found between, highly trained athletes, recreational exercisers, and non-exercising controls, indicating various levels and types of exercise influence bone mass (Nilsson & Westlin, 1971).

The extent of bone hypertrophy is related to the amount and type of stress exerted by the sports activity (Smith & Gilligan, 1987; Jones et al., 1977; Huddleston et al., 1980). For example unilateral physical activity, such as tennis and baseball show that the playing, or dominant arm has a greater bone density than the non-dominant arm (Smith & Gilligan, 1987; Jones et al., 1977; Huddleston et al., 1980). In athletes bone density was

found to increase with an increased load as determined by the type of sport (Nilsson & Westlin, 1971).

Three cross-sectional studies are reviewed which focus on the bone mass differences between athletes compared to sedentary controls. Thirty male marathon runners were found to have 11% greater total body calcium compared to 16 age matched controls, while BMC at the non-exercised distal radius was not significantly different (Aloia, 1978). Dalen and Olsson (1974) also found increased BMC in 15 middle aged (50-59 years) long-term, cross country runners, when compared to 24 matched controls. They had a 20% higher appendicular and 8.5% higher axial BMC. A more recent study by Lane et al. (1986) measured lumbar spine bone density in male and female long distance runners, who had been training for an average of 9 years. Lumbar bone mass was significantly higher in the women (35%) and men (44%) runners than age and sex-matched controls. The study sample was an older population (range 50 - 72 years), suggesting that long-term weight-bearing exercise slow the rate of trabecular bone loss. These studies generally support the conclusion that habitual physical activity leads to a general overall increase in bone mass.

Bilateral symmetry reflects symmetrical use, whereas activities that involve greater use of the limbs on one side result in the bone of that side becoming larger (Lanyon, 1984). Unilateral activity and bone hypertrophy was measured by Jones et al. (1977) in 84 female and male professional tennis players. There was pronounced hypertrophy of the humerus of the playing arm compared to the non-playing arm (control arm). In 35 male tennis players (age 70-84 years) who had been playing tennis for 25 to 72 years, Huddleston and co-workers (1980) found a 13% difference in the BMC of the mid-shaft radius between the playing and non-playing arm. Both of these studies strongly support the conclusion that exercise promotes bone hypertrophy.

In an early study on athletes and bone mass, Nilsson and Westlin (1971) found femoral bone density, measured by photon absorptiometry, to be directly related to the

load placed on the lower limb during a particular sports activity and training program. The athletes in this study showed bone hypertrophy in relation to their specific athletic activity. For example, in descending order of bone mineral mass gain the athletes were weight lifters, throwers, runners, soccer players and swimmers. Swimmers, however, showed no evidence of increased mineralization, and tended to be similar to controls with respect to distal femur bone density. Increased bone density appeared to be a response to weight bearing activity. Of the 64 athletes, 9 were top ranked (international level) and found to have a higher bone density than the "ordinary" athletes, however, one third of these elite athletes had used anabolic steroids.

Conclusions that can be drawn from these cross-sectional studies are: (1) long-term involvement in a physical activity results in greater bone mass as compared to sedentary subjects; (2) the intensity and level of competition (e.g. elite vs recreational) influences bone mass; (3) weight-bearing forms of exercise result in the greatest increase in bone mass; (4) specific bones in the body, if stressed over a number of years, will increase significantly in density (i.e. unilateral sports).

Overall a positive influence of exercise on bone mass is evident from subjects who engage in regular, long-term activity, and this exercise may have a systemic effect. Longitudinal studies must be analyzed to determine the effects of "training" on bone mass to avoid the inherent biases of the cross-sectional studies. The decision of individuals to enter certain types of sports, and their ability to remain in the program, may be dependent on the subject's bone density. For example, an individual with a heavier skeleton may be more successful at weight-lifting, whereas a lighter framed individual may tend towards such activities as swimming or ballet. Therefore, comparison among athletes within different sporting activities may not be valid.

1.8.5 Excessive Exercise

Exercise in moderation seems to be beneficial, however, excessive exercise may be detrimental to the skeleton. Intense physical training may lead to amenorrhea in female athletes, and secondary to this hypoestrogenic state is a significant reduction in axial bone density (Schapira, 1988). This demonstrates that strenuous exercise in a state of estrogen deficiency does not protect against bone loss, and therefore indicates the strong dependence of bone retention on maintaining physiologic endogenous estrogen levels. In amenorrheic athletes vertebral bone mass is reduced relative to both eumenorrheic athletic counterparts and sedentary controls. BMC of the radius, however, does not seem to be affected by menstrual status (Smith & Gilligan, 1987). This finding suggests that exercise does not protect against trabecular bone loss in the absence of estrogen (Dalsky, 1987).

One of the clinical findings of anorexia nervosa is amenorrhea, however, when such hypoestrogenic women exercise, they have a higher bone mass than their counterparts who do not exercise (Dalsky, 1987). Runners who were previously amenorrheic, but became estrogen-replete (i.e. resumption of menses) were reported to have increased vertebral bone density (Dalsky, 1987).

The etiology of exercise-induced amenorrhea has not been conclusively established. Estrogen-depletion once considered the most likely explanation, may not be the only factor influencing bone loss; a compromised nutritional status (e.g. low calcium intake), intense training program, or low body fat may also play significant roles. This relatively new area of study is ongoing; considering that up to 60% of competitive female runners are amenorrheic (Smith & Gilligan, 1987), research to determine an exercise prescription to avoid amenorrhea and ensuing bone loss is of great importance.

Both Margulies et al. (1986) and Leichter et al. (1989) studied the effects of 14 weeks of intense physical training on bone mass in military recruits (age 18 to 21 years).

Both of these studies showed a significant increase in bone mass of the lower limbs in these young male adults over a short period of time. However, approximately 45% of the recruits were unable to train continuously due to stress fractures. From the relatively high frequency of stress fractures these studies indicated that the upper permissible limits of physical exertion is training 8 hours per day, 6 days per week with additional weight being carried.

1.8.6 Exercise Intervention Studies in the Normal Female Population

Cardiovascular fitness can be improved to the same degree by a number of very different activities; for example, walking, swimming, cycling or jogging, if they are performed at the same relative intensity. These same exercises have different effects on bone mass because the local strain patterns they produce in bone are dissimilar. For example spine density is less affected by swimming than running. Cross-sectional studies have shown that the degree of bone hypertrophy is related to the magnitude of the dynamic strain produced by various physical activities. In prospective exercise intervention studies reduced bone loss and bone hypertrophy have been observed in a normal, non-athletic population There are a number of prospective longitudinal studies concerning the effects of exercise programs on skeletal mass in women, however, before these are reviewed four cross-sectional studies that focus on the level of physical activity and its relationship to bone mass will be summarized. Two of these studies use a level of physical activity obtained through a questionnaire, while the other two depend upon fitness and/or activity level determined by a waist monitor.

1.8.6.1 Cross-sectional Exercise Research

Stillman et al. (1986) reported a significant relationship between BMC in the radius mid-shaft and level of physical activity as measured by an activity profile questionnaire, supporting the hypothesis that physical activity inhibits bone loss. A larger BMC was found in women involved in higher levels of physical activity, but no BMC

was found between moderate and low activity levels in women. It was suggested that a "threshold" level of activity is necessary before changes in bone mass occur.

Oyster et al. (1984) correlated physical activity level by questionnaire to the degree of osteopenia in women (60-69 years old). The second metacarpal cortical diameter in the non-dominant hand was measured and significant relationships with activity level and estrogen use were found. The 10 most active women were compared to the 10 least active; the active women had significantly larger cortical diameters, and the authors concluded that physical activity is an important factor for the retardation of osteoporosis.

Pocock et al. (1986) studied the relationship between physical fitness and bone mass (femoral neck, lumbar spine, & forearm) in 84 women, aged 20-75 years (46 were postmenopausal) . Femoral neck and lumbar BMD significantly correlated with fitness (predicted by oxygen uptake on the bicycle ergometer) and to variations in the level of physical fitness. For the 46 postmenopausal women in the study, fitness was the only significant predictor of femoral neck BMD. Aloia et al. (1988) reported that the level of physical activity in sedentary women may be a determinant of peak bone mass and bone density in the spine. Twenty-four healthy premenopausal women (mean age 39 years) had physical activity levels measured over a 3-day period by an activity monitor. Activity level was found to be significantly correlated with total body calcium as measured by neutron activation analysis, and bone density of the spine as measured by DPA, but was not significantly correlated with radial BMC, although this may have been due do the location of the activity monitor. The small sample size (n = 24) in this study did not permit any definitive conclusions to be drawn. However, these studies indicate that higher levels of physical activity are associated with larger bone density. In general longitudinal studies are more useful than cross-sectional studies since the effects of a particular form of training can be followed. It is also difficult to determine what is actually being measured in cross-sectional studies; it may be more than just the effects of exercise, especially when comparing athletes to non-exercising controls. Difficulty in

quantifying the level of activity through questionnaires, and subjective perceptions of effort and energy output are additional drawbacks to cross-sectional investigations.

1.8.6.2 Longitudinal Exercise Research

Longitudinal exercise studies performed using non-athletic, pre- and postmenopausal women have involved a variety of exercise forms including: walking, jogging, basic or standardized program (warm-up, conditioning, circulatory exercises), aerobics, stair climbing, strengthening exercises and/or a combination of any of the these activities. The earlier studies tend not to have the exercise prescription individualized or detailed (i.e. reaching a target heart rate) as in the later ones. The studies reviewed are in chronological order. Table 1.5 provides a summary of the studies.

Studies of exercise effects on the skeleton in humans started in the early 1970s. One of the first studies to quantify the effects of a physical activity program on BMC was reported in 1974 by Dalén and Olssen. Over a 3 month period they studied the effects of walking (n=10, 5 times per week, 3 km), and running (n=9, 3 times per week, 5 km) on 19 male office employees, age 25-52 years. Nine measurements sites were selected to obtain values for cortical and trabecular bone in the axial and appendicular skeleton. Despite an 11% increase in maximum oxygen consumption there was no increase in BMC over the 3 months of training. They concluded that it may be impossible to obtain a rapid increase in BMC. However, it is now known that a 3-month study period (about one remodeling period for adult bone) is insufficient to allow for significant new bone formation (Frost, 1988). A major limitation with the work of Dalén and Olssen was the precision and accuracy of the bone mass measurement techniques available.

Since Dalén and Olssen's work in 1974 a number of research investigations have been undertaken studying the effects of planned exercise programs on the bone mass of older women. These studies have been carried out primarily during the last 10 years with the majority reporting improvements in bone status after exercise intervention.

Table 1.5 Summary of Longitudinal Studies on the Effect of Exercise on Bone Mass in Older Women

Reference	Age (range) years	Groups	Duration months	Measure	Site	Results	
						Treatment	Control
Aloia et al., 1978	53	Calisthenics & light aerobics (n=9) Control (n=9)	12	SPA IVNAA	radius total body calcium	0% (NS) +2.6%(NS)	0%(NS) -2.5% (P<.001)
Chow et al., 1987	56 (50 - 62)	Aerobics (n=33) Aerobics & Strength (n=16) Control (n=15)	12	IVNAA	trunk & thigh	+8.0% +4.2%	-1.1%
Cavanaugh & Cann, 1988	(49 - 64)	Walking (n=8) Control (n=9)	12	QCT	lumbar spine	-5.6% (P<.005)	-4.0% (P<.01)
Dalsky et al., 1988	(55 - 70)	Aerobics (n=17) Control (n=18)	9	DPA	lumbar spine	+5.2% (P<.005)	-1.4% (NS)
		Aerobics (n=11) Control (n=14)	22	DPA	lumbar spine	+6.1% (P<.001)	-1.1% (NS)
Krolner et al., 1983	61 (50 - 73)	Calisthenics, walking, running (n=16) Control (n=15)	8	DPA SPA	lumbar spine radius	+3.5% (NS) 0% (NS)	-2.7% (P<.05) -3.7% (P<.05)
Sandler et al., 1987	58 (49 - 65)	Walking (n=114) Controls (n=115)	36	CT	radius	-3.7% (P<.01)	-3.7% (P<.01)

Table 1.5 Summary of Longitudinal Studies on the Effect of Exercise on Bone Mass in Older Women **(continued)**

Reference	Age (range) years	Groups	Duration months	Measure	Site	Results	
						Treatment	Control
Simkin et al., 1987 (Ayalon et al., 1987)	63 (53 - 74)	Dynamic bone loading (n=14) Osteoporotic controls (n=26)	5	SPA Compton Scattering	distal radius distal radius	-3.3% (NS) +3.8% (P<.01)	+3.1% (NS) -1.9% (P<.02)
Smith et al., 1981	83 (69 - 95)	Seated calisthenics & light aerobics (n=10) idem + calcium & vitamin D (n=11) Control (n=18) idem + calcium & vitamin D (n=12)	36	SPA	radius	+2.3% (P<.05) -0.3% (NS)	-3.3%(NS) +1.6% (P<.05)
White et al., 1984	(50 - 63)	Walking (n=36) Aerobic Dance (n=36) Control (n=24)	6	SPA	distal radius	-1.7% (P=.005) +0.8% (P>.05)	-1.6% (P<.005)

Aloia et al. (1978) observed the effect of exercise (moderate intensity for one hour, three times per week) on total body calcium and BMC of the distal radius in nine postmenopausal women over a one year period. Total body calcium was found to increase significantly in the exercise group. In nine age-matched sedentary control subjects total body calcium decreased. The BMC of the radius did not change in either group, but the authors suggest changes in an appendicular bone site may not reflect changes in the total skeleton. The failure to observe radial BMC changes may also have been due to the relative insensitivity of cortical bone to exercise challenge. Calcium intake was not controlled in this study, however, dietary histories indicated there was no change in calcium intake over the study period.

Krølner et al. (1983) studied healthy women, aged 50-73 years. The exercise group participated in a standardized exercise program for 1 hour, twice a week over an 8 month period. A 3.5% increase in the lumbar spine BMD, measured by DPA, was observed in the exercise group, while the control group decreased by 2.7%. No significant changes in BMD were observed in the distal radius in either group. The researchers concluded that physical exercise may prevent spinal osteoporosis.

Smith et al. (1981) measured radial BMC by SPA in female nursing home patients (aged 69-95 years). The physical activity group regularly participated in light to moderate intensity exercise program, 30 minutes per day, three days per week for 36 weeks. BMC of the radius increased 2.3% in the exercise group and declined 3.3% in the controls.

The effects on bone loss of a 3-year walking program in postmenopausal women (age 49-65 years old) was studied by Sandler et al. (1987). The shaft of the radius was measured to determine if exercise effects on bone was systemic rather than localized. Bone density losses were found to be comparable in the walking and control group, indicating that walking does not illicit a systemic response on bone density.

Cavanaugh and Cann (1988) monitored the rate of loss of spinal TBD using QCT in a small group (n = 8) of postmenopausal women during a 52-week moderately brisk

walking program. They found that their program — walking 3 days per week, and building up from 15 to 40 minutes per session — did not prevent the loss of spinal bone density in this particular group. It was interesting to find that there was no significant change in fitness level (i.e. body fat, post-exercise heart rate) over the exercise duration.

White et al. (1984) studied the effects of both walking (1 to 2 miles, 6 days per week), and aerobic dancing (2 to 5 dances, 6 days per week) in 73 postmenopausal women by measuring the distal radius BMC by SPA. The study period was only 6 months, however, the results showed that the controls and walkers lost a significant amount of BMC while the dancers maintained their BMC. Without specific loading exercises directed to the forearm, it was surprising that the dancers maintained BMC at that site. Based on the short study duration, and the poor precision of the bone mass measurement techniques employed these result cannot be considered representative.

Chow et al. (1987) studied the effect of two exercise programs (aerobics, and aerobics plus strengthening exercises) on bone mass in 48 healthy postmenopausal women, age 50-62 years, over a one year period. After one year of intervention both exercise groups had greater bone mass (IVNAA measured by neutron activation analysis) compared to controls. The supplementary muscle strengthening program had no obvious additive effect on bone mass. This study suggests that exercise can modify bone loss in healthy postmenopausal women.

Dalsky et al. (1988) studied the effect of weight-bearing exercise training and detraining on lumbar BMD in 35 healthy postmenopausal women, age 50 - 70 years old. The exercise training was either for 9 months (short term) or 22 months (long term) and involved walking, jogging and stair climbing at an intensity of 70 to 90% of VO_2max, three times per week for 50 to 60 minutes per session. Over the 9 months training period the BMD of the lumbar spine, measured by DPA, was significantly increased (5.2%, range 2%-8% above baseline), while there was no change in the controls. With the long term exercise program a 6.1% (range 3.9 to 8.3% above baseline) increase was

measured. At the conclusion of the detraining phase BMD was found to be only 1.1% above baseline values. It was concluded that BMD can increase significantly above baseline levels with training, however if training stops, the BMD will revert to pre-exercise baseline levels.

Smith et al. (1989) conducted a 4 year exercise intervention program in middle-aged women. Eighty subjects (mean age 50 years) exercised three times per week for 45 minutes each session. Bilateral measurements BMC of the radius, ulna and humerus were made. The rate of BMC loss in the exercise group was significantly less than that in the control group. The greatest effect of the exercise intervention was found in the ulna and radius. Differences in response between pre- and postmenopausal subjects were investigated to determine the effects of menopausal status on exercise response. Exercise subjects were found to have a lower rate of bone loss, regardless of menopausal status. It was concluded that physical activity significantly reduces bone loss in the forearms of middle-aged women.

Smith (1989) studied the effects of aerobic exercise on both premenopausal and postmenopausal women (ages 35-65 years) to determine if the effects of exercise are independent of hormonal status. The exercise program comprised aerobics and upper and lower body activities, three 45-minute sessions per week. Both groups of women had significantly reduced bone loss and no significant differences in bone response to exercise. This study provides evidence that the effects on bone of the mechanical control system and hormones are independent.

Two studies involving bone-loading exercise have been completed [Simkin et al., 1987 (Ayalon et al., 1987); Rockwell et al., 1989] Simkin et al. (1987; Ayalon et al., 1987) studied 14 osteoporotic women (mean age 63 years) who performed bone-loading exercises for the distal radius, three times a week for 5 months. Although the distal radius bone density measured by Compton scattering did increase (3.8%), the BMC of cortical bone measured by SPA did not change. This indicates a greater, and perhaps a

more rapid change in trabecular bone than in cortical bone. Rockwell et al. (1989) studied 12 "pre"menopausal women (mean age 36 years) over a 4-month period on a weight-training program. The strength increased by 57 ±8%, however, they found no change in vertebral or femoral bone mass measured by DER, after training 2 times per week at 70% of one repetition maximum (2 sets, 12 repetitions per set). This study is also limited by its short duration; four months is too short a time period for measurable change in bone mass to occur.

In general the consensus from the exercise studies cited exercise training appears to significantly reduce age-related bone loss.

1.8.7 Theories of Exercise Effects on Bone

The mechanism for bone mass increase in response to dynamic loading is not well understood, although several theories have been put forward. One theory suggests mechanical loading on the adult skeleton may inhibit bone remodeling and result in the maintenance of the skeleton. A form of bone growth may then occur through mini-modeling at the site where stress is applied. The threshold which initiates bone remodeling may be increased, so it requires greater strain on the bone before remodeling will occur. When loading is removed, mini-modeling stops, remodeling is released from inhibition and loss of bone can occur (Overton, 1987).

In human cortical bone at about 25,000 μE *in-vivo*, fractures are possible in longitudinal tension or compression (Frost, 1988). However, in the most vigorous voluntary, human physical activity about 1500 μE to 3000 μE is generated which is only one tenth of the fracture strain threshold in tension or compression. Strains above 1500 μE enables modeling and additions of new cortical bone, while a much smaller threshold strain range, 100 μE to 300 μE, exists for mechanical control of remodeling. The responses of mechanically controlled bone modeling and remodeling to mechanical usage (i.e. exercise) are opposite, but their overall effects are similar. For example, with

increased mechanical usage modeling increases resulting in gains in bone mass, while remodeling is decreased which in turn reduces bone mass losses. The remodeling response differs from modeling because only 100 μE to 300 μE depresses remodeling, which conserves existing trabecular bone, cortical-endosteal bone and retards cortical thinning (Frost, 1985). Where modeling is enabled by overloading, remodeling increases in response to underloading.

Mechanically controlled adaptation of bone is thought to be dependent on the largest, daily repeated dynamic loads (and hence strains) experienced (Frost, 1988). For a mechanical load to send a signal to the bone cells that they can perceive and respond to, a transducer (i.e. a mechanism that can change input energy of one form to output energy of another) that can control a system's behavior must exist (Frost, 1988). One mechanical transducer is interstitial fluid flow. Loads placed on the bones result in tissue strain and in turn an electric potential, and certain transient chemical effects of strain-induced flow of interstitial tissue fluids occur. A substantial body of evidence indicates that electricity can induce bone formation (Sinaki, 1989). The mechanical usage of a tissue would be converted to corresponding cell signals that could detect and respond to them. Mechanical usage may also affect the system through changes in local blood flow and interstitial fluid pressure gradients and their magnitude and possibly mechanical stresses in the tissue matrix (Frost, 1988).

Lanyon (1984) found that only a few strain cycles were required to produce increases in bone density in animals which suggests a specific response is induced within a receptive cell population rather than an indirect effect such as tissue damage or increased perfusion.

Mechanically controlled remodeling adaptations occur slowly (as the remodeling period is 2 to 4 months depending whether cortical or trabecular bone is considered), however, this has been challenged by aggressive athletes and boot camp trainees with the result of such problems as stress fractures and shin splints.

1.8.8 Recommendations for Exercise Programs

Weight-bearing physical activity has been recommended as a therapeutic intervention to prevent osteoporosis. The perception that involvement in exercise is generally "healthy" has led, in part, to ad hoc exercise recommendations without specific guidelines.

The four basic components of any exercise program follow the FITT principle: F = the frequency with which exercise is to be performed; I = the intensity of that exercise; T = the duration of each session, and T = the type of exercise. Individualization must also be planned, such that base fitness level, and physical limitations are taken into account.

In animals a "threshold" of activity has been observed. Above a lower activity level changes and adaptation in bone occurs, but beyond a maximum stimulus level no further improvement is seen. This finding indicates that frequency, intensity and duration of strain application are important in modifying bone mass. When duration for a training program is considered the bone remodeling period (4-6 months), should be taken into account. It has been recommended that a training period extended over two to three times bone remodeling periods (10-15 months) to ensure that the training effect is measured after a new equilibrium level has been attained (Dalsky, 1987).

Since many questions remain concerning the effects of exercise on bone, it is difficult to make specific recommendations for exercise programs, however, a few general conclusions can be drawn. It is best for the physical activity to be weight-bearing as bone density in swimmers, unlike other athletes, does not differ significantly from non-athletes (Nilsson & Westlin, 1971). Therefore, weight-bearing activities, such as running, tennis, or aerobics should be used. However, individuals who have, or who are at risk of osteoporosis, and those starting at a low fitness level, may benefit more from low-impact activities. Muscle tension induces loading in bone which appears to have

local rather than systemic effects, and dynamic loading stimulates bone remodeling, and conserves bone, whereas static or compressive forces do not. To conserve bone the activity should be vigorous enough to produce a high peak strain and strain rate, and should include a wide variety of loading situations. It appears from reported data that 2-3 hours per week of exercise may be effective in reducing rate of bone loss, and in some individuals bone hypertrophy may result at this exercise level. Exercise programs, although difficult to implement and to maintain compliance, have benefits that are far reaching. If conducted carefully they can improve overall health and well-being, and through increased agility and co-ordination decrease the risk of falling and subsequent fracture.

1.9 Purpose of Thesis

No prospective longitudinal clinical trials using a specific weight-training form of exercise in older women to reduce the rate of bone loss and to compare the relative efficacy of exercise to the effects of HRT on bone mass have been reported. However, weight-bearing forms of exercise are routinely recommended in the prevention and treatment of osteoporosis since there is a perceived positive association between physical activity and "well being" which extends to the skeleton.

From cross-sectional and prospective longitudinal exercise research in females results suggest, in general, that exercise increases bone mass even though many of these studies used general aerobic fitness programs and measured non-exercised bone sites. The available data are inadequate for a definition of an exercise prescription to maintain or increase bone mass, or even reduce the rate of loss for the prevention of osteoporosis. The literature review confirms that our present understanding of specific exercise prescription for postmenopausal women for maintenance of bone mass is poor. However, from available research on mechanical usage of the skeleton, from immobilization through to elite athletic activities, and from animal studies, two principles

in an exercise program emerge: (1) loading the skeleton using weight-bearing forms of exercise and, (2) direct stimulation and loading of the muscles around the bone site of interest.

The purpose of this pilot clinical trial was therefore to determine if bone mass could be maintained through a specific form of weight-training exercise in healthy postmenopausal women, and if this exercise response was as effective as hormone replacement therapy for this purpose. The particular exercise program developed used both weight-bearing through the use of weights, and specific stimulation of muscles around the bone sites of interest.

Chapter 2: Experimental Design and Methodology

2.1. Overview

Healthy postmenopausal women were recruited to a 2-year pilot clinical study of relative efficacies of a specific weight-training program and of hormone replacement therapy (HRT) on the rate of bone loss. Three study groups were established, a control, an exercise, and a HRT group. All subjects had calcium intake standardized by dietary manipulation and/or calcium supplement. Each subject in the exercise group was provided with home-based exercise equipment for arms and legs. HRT consisted of either oral or transdermal estrogen used in conjunction with a progestogen, if appropriate.

Upon acceptance into the study informed consent was obtained and clinical screening performed. Clinical screening included a physical examination, medical history, bone mass screening and clinical laboratory testing. Baseline data was collected for bone mass, nutrition and fitness parameters. All measurements were taken at 6-month intervals with the exception of two fitness parameters which were measured annually. An overview of the study design is shown in Figure 2.1. Bone mass was measured at three sites, the distal radius, lumbar spine and proximal femur. A nutrition questionnaire, diet history and calcium assessment were obtained at baseline only, while three-day food records were obtained at regular intervals. Fitness evaluation included: a physical activity questionnaire, a bicycle ergometer stress test to measure peak oxygen consumption, anthropometric measurements, and strength testing. Clinical laboratory tests included routine blood and urine analyses, and special reproductive and calciotrophic hormone assays.

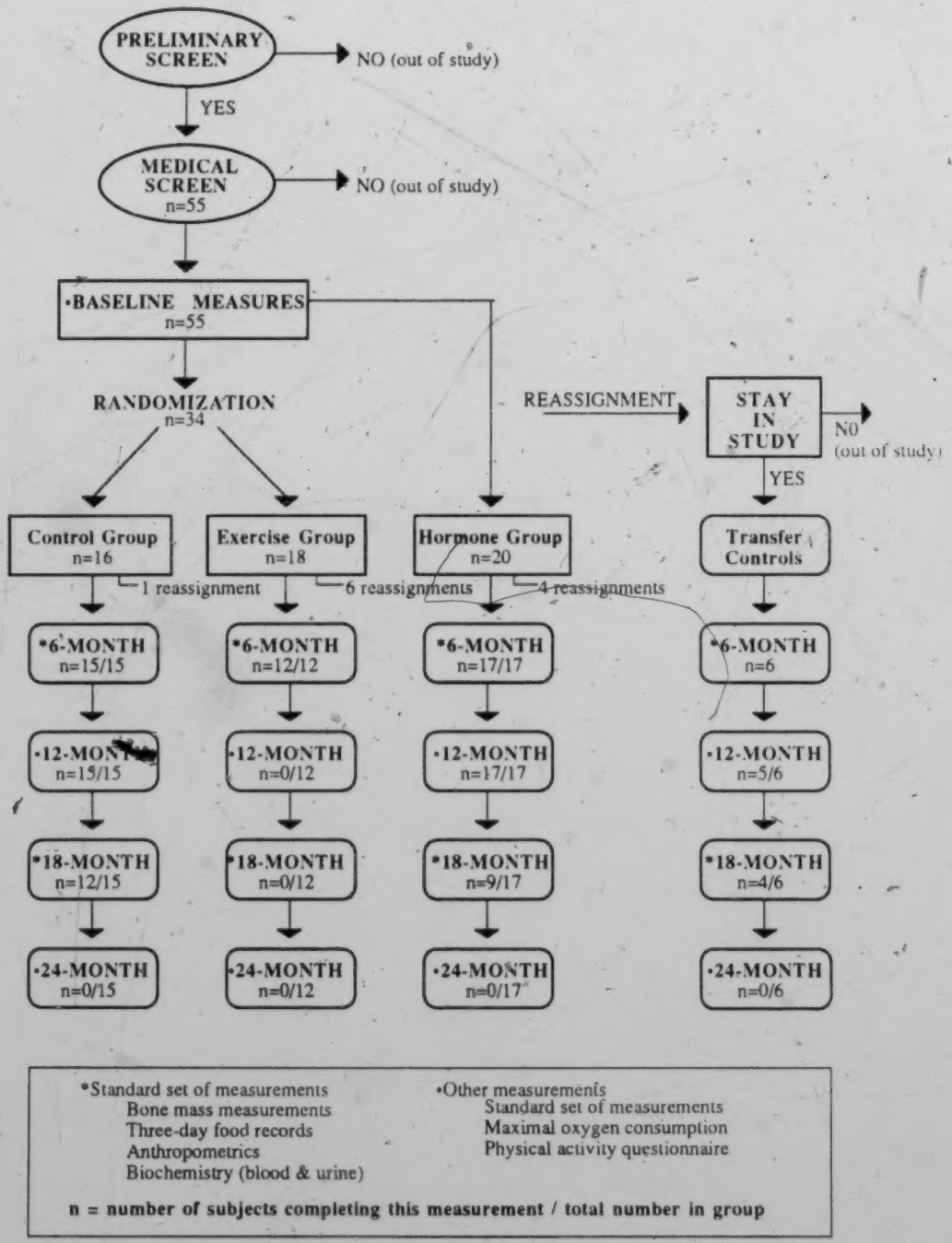

Figure 2.1 Overview of study design[2]

[2]Based on data as of November 1st, 1989.

2.2. *Introduction*

The duration of the study was set for 2 years with an endpoint in 1990 and thus only preliminary data was available for this thesis. Although this report has major emphasis on the exercise component of the study, the experimental design and methodology for the complete study is included so that the limited data available could be presented within the context of the complete study.

2.3. *Experimental Design*

The statistical design was based upon a repeated measures analysis of variance over the two year period.

2.3.1. *Sample Size*

Sample size requirements were based on changes in bone density in the distal radius, lumbar spine and proximal femur over a 2 year period in the control subjects. Previous accumulated data suggested mean changes over this time period of 4% at the distal radius (TBD), 6% at the lumbar spine (BMD) and the proximal femur (BMD). The standard deviation (σ) of the change in bone mass was estimated at $\pm 3\%$ for the three sites.

The formula used for the sample size estimates was (Snedecor & Cochran, 1976):

$$n = (Z_\alpha + Z_\beta)^2 \, \sigma_D^2 \, / \, \delta^2$$

α was set at 0.05 and β at 0.2. The effect size delta (δ) that was considered clinically important was estimated from previously reported studies. An estimated difference in bone mass between the control and treatment groups of 3% was accepted as a significant result at the 95% confidence level.

Substituting these values into the sample size equation, and using a two-tailed test, a sample size of 13 subjects was needed in order to observe a clinically significant result

over the two year period. Compensating for an estimated 15% drop-out rate each group required a minimum of 15 subjects.

2.3.2. *Study Design*

The study design required three study groups to be measured repeatedly over time. Treatment was instituted at baseline, with measurements made at each 6-month interval over 2 years (Figure 2.2). Details of the data analysis are provided in section 2.12.

Study entry (0 month)	Test 1 (6 month)	Test 2 (12 month)	Test 3 (18 month)	Test 4 (24 month)
Control	X	X	X	X
Exercise	X	X	X	X
HRT	X	X	X	X

Figure 2.2 Study design

2.4. *Subjects*

Fifty five healthy postmenopausal women (54 Caucasian, 1 Oriental), age 50-57 years were entered into the study. All women were within 1-5 years of natural menopause, defined as absence of menses for 12 months, and had a FSH (follicle stimulating hormone) level >40 IU/L (Speroff et al., 1983).

All subjects were from Edmonton and surrounding areas. Recruitment was through local advertising (i.e. community newspapers, women's groups, hospital newsletters, posters throughout the city of Edmonton), and through offices of local Obstetrics and Gynecology specialists.

Three study groups were established: (i) control, (ii) exercise, and (iii) HRT. The first two groups were formed through random assignment; subjects in the third group had recently started, or were about to start hormone replacement therapy

2.5. *Screening*

Preliminary screening of all volunteers was by telephone contact with the research nurse who excluded respondents who clearly did not satisfy general inclusion criteria or who decided not to participate upon learning more about the study. General inclusion criteria took into account appropriateness of age, menopausal status, general health, no history of any form of hormone replacement (either orally or topically), and a willingness to participate over a two year period with regular visits to the Bone Research Unit at the University of Alberta.

Following the preliminary screening clinical screening was done. First, a Study Information sheet (Appendix A) outlining the purpose and general format of the study, and an Informed Consent (Appendix B) were provided to each subject to take home and read at her leisure. Subjects were encouraged to ask questions prior to signing the Consent form. Medical screening followed. This involved a medical history emphasizing osteoporosis risk factors (e.g. stature change/lifestyle, etc.), clinical examination by a physician, bone mass screening and clinical laboratory testing to confirm that each subject satisfied the study entry criteria (Appendix C).

Bone mass in the distal radius was measured using gamma-ray computed tomography (γ-CT) to confirm that bone density was above a threshold of 0.125 g cm^{-3}, a lower limit based upon the sensitivity of our measurement method.

2.6. *Assessment of Nutritional Status*

Due to the importance of diet on the bone health, detailed nutrition information was collected. All data were collected using an interview technique unless otherwise indicated.

2.6.1. Diet History and Nutrition Questionnaire

A diet history and general nutrition questionnaire were completed at baseline, subjects were asked to recall all the foods and beverages consumed during a "typical" day. The general nutrition questions involved past and present dieting practices, body weight history, food and nutrient supplementation use, meal pattern, use of snacks, frequency of eating out, usual food preparation practices, and history of food allergies (Appendix D).

2.6.2. Calcium Assessment Form (food frequency)

Dietary calcium intake was assessed at baseline through a food frequency questionnaire (Appendix E), which provided a quantitative estimate of an individual's average calcium intake. Food models were used, as appropriate, to aid in subject recall of the portion size of foods consumed. Food frequency (e.g. daily, weekly, or monthly) and the quantity consumed was determined. The calcium assessment form included 45 foods, which were either high in calcium (e.g. milk, cheese), or those foods usually consumed in larger portions (e.g. bread) which contribute significantly to the total calcium intake. This information was used to estimate the initial amount of calcium supplementation required.

2.6.3. *3-Day Food Record*

Subjects were taught how to keep a food record, and then asked to record the amount and type of food eaten over a 3-day period (Appendix F). The 3-day food record included two week days and one weekend day, and was recorded at 6-month intervals over the 2-year study. Food scales (250 gram, 9 oz, Soehnle combi) were provided to each subject, unless they had their own. Food scales were the most common measurement tool used, however, other tools such as measuring cups, teaspoons, etc., were also used for recording portion sizes. The food record was then entered into the

computerized University of Alberta Human Nutrition Database (Appendix G) and analyzed for its nutritional adequacy. In total forty nutrients were assessed.

The 3-day food record was used to establish customary calcium intake level for each subject. The average calcium intake was compared to the level determined from the calcium assessment form (Section 2.5.2) to decide upon the appropriateness of calcium supplementation.

Each subject was provided with feedback on the nutritional adequacy of their diet by a print-out which was part of the computer program. This program documented the appropriateness of various nutrients based on the Recommended Nutrient Intakes for Canadians (RNI) for example: total energy intake, fibre, sodium. Written suggestions were also provided to subjects concerning specific dietary improvements. The dietitian was in contact with all subjects during the course of the study to answer questions, and to advise and provide individual feedback from the food records. This personal contact and information feedback was found to be a valuable component in maintaining compliance with the study protocol.

2.6.4. Calcium Supplementation

For all subjects calcium intake was standardized at approximately 1500 mg of elemental calcium per day and was monitored through regular (i.e. every 6-month) 3-day food records. Calcium intake of 1500 mg day^{-1}, in postmenopausal women was recommended by the National Institute of Health consensus conference (1984). Subjects who required calcium supplements were provided with effervescent tablets. If these were not tolerated then either chewable or capsule forms of the supplement (Sandoz Canada Inc.) were also available. The effervescent tablets were formulated as calcium lactate gluconate and calcium carbonate and were considered the better vehicle for biological availability of calcium from the gut; the capsules and chewables were formulated as calcium carbonate.

Subjects with initial calcium intakes between 400 to 600 mg day^{-1} were provided with a daily supplement of 1000 mg elemental calcium; for initial calcium intakes between 600 to 850 mg day^{-1}, 850 to 1100 mg day^{-1}, and 1100 to 1125 mg day^{-1}, supplements were 750, 500 and 250 mg day^{-1} respectively. When calcium intake from diet alone was between 1250 to 1500 mg day^{-1} no supplement was provided.

2.7. *Physical Fitness Parameters*

Measures of physical fitness were required for two main reasons: (1) to determine change resulting from a specific weight-training program, and (2) to determine the influence of body composition, strength and activity level on bone density.

All fitness parameters were measured at 6-month intervals with the exception of the exercise stress test and the physical activity questionnaire which were measured annually.

2.7.1. *Anthropometrics*

Height, weight, skinfold, and girth measurements were made in accordance with the procedures set out by the Canadian Standardized Test of Fitness (CSTF) Operations Manual (1987, 3rd edition).

2.7.1.1. *Standing Height*

A Health-O-Meter (Continental Scale Corp., Chicago, Ill.) with a metric ruler was initially used to measure freestanding height. Height was recorded to the nearest 0.5 cm. It was later determined that the Health-O-Meter height scale was inadequate for our height measurement, and a simple apparatus was constructed using a wall-mounted tape measure and wooden right angle; height was measured with a precision of ±0.2 cm.

2.7.1.2. *Body Weight*

A Health-O-Meter scale was used to measure body weight to the nearest 0.1 kg. Subjects did not wear shoes but were fully clothed. During the study, weight was taken

at various times throughout the day depending on the time of the subjects scheduled appointment. Using calibrated weights (10 kg to 80 kg, at 10 kg increments) the accuracy of the scale was determined. It was found to be accurate over the range of 10 kg to 60 kg. Between 70 kg and 80 kg, however, errors of approximately 0.05 kg and 0.1 kg, respectively were found. No correction of subject weight was made for these small errors.

2.7.1.3. Girth Measurements

A flexible, millimeter scale plastic tape was used to measure girth. Measurement sites were located according to the CSTF, with some small modifications, and measured to the nearest 1 mm. Four girth measurements were made in addition to three other measurements (relaxed and flexed arm girth, and calf girth) which are not a part of the CSTF protocol (Appendix I). All girth measurements were made on the right side of the body with the subject standing erect, with the exception of the calf girth which was taken with the subject sitting. Tape positioning was maintained without depressing the skin surface. Thin clothing was worn for the gluteal girth measurement (i.e. underwear) and occasionally nylon stockings were kept on for gluteal, thigh and calf measurements.

2.7.1.4. Skinfold Measurements

Hemco calipers (Holland, Michigan) were used to measure skinfolds. The caliper dial had scale increments of 2 mm, with measurements being interpolated to the nearest 1 mm. All five skinfold measurements were taken on the right side of the body following the CSTF procedures (Appendix J). The skinfold measurement procedure was repeated until two successive measurements were no more than 4 mm apart, and then the average of these was recorded.

2.7.2. Fitness Testing

Exercise stress tests were used to determine the subjects' peak oxygen consumption. Subjects participating in the exercise group may tend to be generally more

active with their discovery of the greater muscular strength and endurance that will develop over time in the program resulting in increased aerobic capacity. Also, studies have observed a relationship between bone mass and various fitness parameters, i.e. oxygen consumption, muscle strength, muscle mass and fitness level.

2.7.2.1. Exercise Stress Test

A symptom-limited, graded exercise stress test to determine aerobic performance was performed annually using a cycle ergometer (Model 38B, Siemans Ltd.) located in the University of Alberta Hospitals Stress Testing Unit (Division of Cardiology). Each test was carried out under the supervision of a cardiologist. Specifically, the peak volume of oxygen consumed (VO_2max) during the test was measured. The initial workload was set at 15 Watts (W) and a cadence of 50-60 rpm (revolutions per minute). After 3 minutes at 15 W the resistance was increased to 30 W, and then raised by 20 W every 3 minutes. The test was continued until one or more of the following end points was reached:

1. when maximal oxygen uptake was attained,
2. a target heart rate of 100% of the age predicted maximum (determined by taking 220 beats per minute and subtracting the subject's age),
3. Borg scale rating of 17 = "very hard", or fatigue or exhaustion
4. inability to maintain a cycling cadence of 50 rpm,
5. signs and symptoms of exertional intolerance were evident (e.g. dizziness, nausea, angina),
6. abnormal electrocardiographic changes (e.g. arrhythmia, ST segment depression or elevation),
7. abnormal blood pressure response.

The reason for cessation of each exercise test was recorded by the cardiologist. A continuous 12-lead electrocardiograph (ECG) was obtained (Marquette Case) during rest, exercise and recovery. A mercury sphygmometer was used to measure blood pressure during the second minute of each stage of exercise and during recovery. Ratings of

perceived exertion were made during each workload level, at approximately the 2.5 minute mark using the Borg scale (Borg, 1970). Each subject wore a nose clip and rubber mouth piece attached via a 3-way valve to an oxygen analyzer.

2.7.2.2. Grip Strength

A Layfayette hand grip dynamometer was used to measure hand grip and forearm strength. The procedures followed were those outlined in the CSTF operations manual. Both hands were measured alternately with two trials per hand. The best score for each hand was taken and recorded to the nearest "kg".

2.7.2.3. Repetition Maximum for Leg Strength

Strength of the lower limbs was determined by one repetition maximum (1 RM) using a specially designed leg-press apparatus (Hydra-fitness Equipment Inc.). For each subject the "warm-up" consisted of 10 repetitions using light weights (approximately 34 kg), followed by a short rest period (30 to 60 seconds) and the addition of a 11.4 kg weight with 10 repetitions. Weight was then increased in 11.4 kg increments with the subject performing only 2 repetitions at each stage, until they felt that they were close to their maximal strength level. Subjects were then asked to perform as many repetitions as they could using that weight. If more than 12 repetitions were achieved subjects rested for 2 minutes before repeating the exercise with an additional weight increment. Since these women were not familiar with weight-lifting techniques we did not expect to find their "true" 1 RM, but rather to find a weight that they could lift no more than 12 times. The weight lifted and the number of repetitions were recorded and 1 RM interpolated (Landers, 1985). The maximal strength was expressed as the "maximal weight lifted", and did not include body mass as a factor. Of 25 plate weights calibrated on the Health-O-Metre scale, 6 were found to be inaccurate (-2.6% to 2.11%).

2.7.2.4. Physical Activity Questionnaire

This questionnaire, (Appendix K) completed by interview, involved both a history of physical activity patterns and present day activities. Details of household activities

(e.g. cleaning, gardening), recreational and sporting activities (e.g. walking, golfing) were recorded. After the initial Physical Activity Questionnaire, self-administered questionnaires (Appendix K) were given annually to determine changes in activity levels.

Questionnaire evaluation allowed the subject to be classified into one of three groups: sedentary, active, or very active (Appendix K). Using the physical activity questionnaire each subject was awarded points based on the amount of involvement in household activities, as well as recreational and sporting type of activities. Achieving a score of 0-4 would classify a subject as sedentary, 5-8 as active and, 9-14 as very active. To be considered very active the individual must have participated in a moderate-high intensity activity, such as swimming or aerobics more than three times a week for over 30 minutes each session for the duration of the year, in addition to regular household activities.

2.8. Bone Mass Measurements

For each subject the absolute change, and rate of change in trabecular bone mass (TBD) in the distal radius, and in bone mineral density (BMD) in the lumbar spine and proximal femur were measured. Gamma-ray computed tomography (γ-CT) was used to measure TBD in the distal radius using well established methods (Hangartner & Overton, 1982). BMD was measured in the lumbar vertebrae and proximal femur by dual energy radiography (DER; Hologic QDR 1000). Bone density measurements were made at baseline and at six-month intervals over the 2 year study period. In all these longitudinal bone mass measures each individual served as their own control and results were expressed relative to pre-treatment values. Cross-sectional data at each time point in the study was used to characterize particular study groups.

2.8.1. Gamma-ray Computed Tomography

At each 6-month time point distal radius TBD was measured twice within a 2-week period by a qualified technologist. Each measurement session was about 25 minutes in duration and involved a radiation dose to the 20 mm site of less than 0.20 mSv (milliSieverts).

The γ–CT scanner was designed by the Bone Research Unit and brought into operation in 1979. This technique provides three-dimensional information on density distribution at a particular bone site, and measures trabecular bone separately from cortical bone.

The scanning and analysis procedures for γ–CT have been reported (Hangartner & Overton, 1982). The precision of the method, based upon phantom studies, was 0.04% (coefficient of variation, CV). In clinical studies the precision has been demonstrated to be better than ±0.6% with the major error contribution arising from repositioning of the measurement site. The accuracy of the method was -0.6 to +3.4% (Hangartner et al., 1987).

2.8.2. Dual Energy X-ray Photon Absorptiometry or Dual Energy Radiography

A Hologic QDR 1000 system was employed to measured total (integral) bone density in the lumbar spine and proximal femur with very low radiation dose and high precision.

At each measurement point bone mineral density (BMD) in the lumbar spine (L1-L4) was obtained with a radiation dose of 0.05 mSv, and a scan time of approximately 8 minutes. For the proximal femur measurement of BMD a radiation dose of 0.05 mSv was also incurred with a scan time of about 5 minutes. In data analysis, regions of interest (ROI) for the spine and for the proximal femur were automatically selected under computer control. The femoral neck, Ward's triangle and the inter-trochanteric region were the specific sites of the proximal femur assessed.

The precision of these measurements is about ±1% (CV) for the spine and ±2% for the proximal femur (Hologic, 1989). The DER system was used in accordance with the manufacturer's specifications (Hologic, 1989) by a qualified technologist, and the results reviewed by a radiologist.

2.9. *Endocrine and Biochemical Measurements*

A standard biochemical profile and specific reproductive and calciotrophic hormone assays were obtained for all subjects. These values were initially used to document normalcy of bone metabolism, to verify postmenopausal status, and subsequently to monitor changes throughout the study.

At 6-month intervals a venous blood sample (50 ml) was obtained and a 24-hour urine sample provided by each subject. Standard blood and urine measurements were made by the University of Alberta Hospitals Clinical Laboratory. Special assays (for some of the reproductive and calciotrophic hormones) will be analyzed at the end of the study.

2.9.1. *Routine Biochemical Tests*

Routine biochemical tests were taken at baseline and at each 6-month point throughout the 2-year study. The variables measured are outlined in Table 2.1.

2.9.2. *Reproductive Hormone Assays*

Blood samples for appropriate reproductive hormones (listed in Table 2.1) were collected at each 6-month visit and frozen for assay at the end of the study.

2.9.3. *Calciotropic Hormone Assays*

Blood samples for calciotrophic hormones (refer to Table 2.1) were collected at baseline and at 6-month intervals, and frozen for assay at the end of the study.

Table 2.1 Endocrine & biochemical measurements

ROUTINE TESTS		HORMONES	
BLOOD	URINE	REPRODUCTIVE	CALCIOTROPHIC
total calcium	calcium	leutinizing hormone	cyclic AMP*
phosphorus	phosphorus	FSH*	PTH*, n-terminal
creatinine	creatinine	estrone	PTH*, mid-molecule
urea	volume	total estradiol	1,25 (OH)2 D*
glucose		free estradiol	25, (OH) D*
ionized calcium		testosterone	osteocalcin (GLA)
magnesium		DHEA*	calcitonin
uric acid		DHEAS*	
alk phos		SHBG*	
AST*			
LD*			
total bilirubin			
total protein			
albumin			

* measurement names are defined under abbreviations

2.10. Exercise Training Program

A simple leg-press apparatus designed in this laboratory was placed in each subject's home (Figure 2.3). Up to 95.5 kg of free-weights for the lower limbs and two hand-held dumbells with free-weights each totaling up to 5 kg were provided to each subject in the exercise program. The leg-press routine and the arm exercises were designed to produce physiological strain levels in the femur, lumbar spine, radius and ulna. The exercise program was taught to the subjects as a group, and later reviewed in the same manner. Safety was a major consideration: to minimize back injury while loading the lumbar spine an inclined supine position was used for the leg-press apparatus. Set-up of the leg apparatus allowed each subject to press the weight through a distance of approximately 25 to 37.5 cm. In the starting position the knees were at 90°, and the exercise involved moving through to full extension, but not locking the joint, then slowly returning to the starting position. The initial amount of weight lifted by the lower limbs was based on individual tolerance and determined by what "felt good". Therefore, the starting weight varied from a minimum of 38% to a maximum of 104% of the subject's body weight.

Figure 2.3 Weight-training apparatus for the lower limbs

Arm resistance was initially supplied using a 2 kg weight with subsequent gradual increments in weight. Five different arm exercises were performed. A handout was provided to each subject outlining how to carry out the required movements safely (Appendix L). The lower and upper limb exercises were to be performed a minimum of 3 days per week, with 5 days per week recommended. There was a gradual increase from one set of 10 repetitions to a maximum of 3 sets of 10 repetitions. The time requirement of the subject for each session was approximately 30-45 minutes including warm-up. Subjects were taught when and how to increase the amount of weight they were lifting (Appendix L).

Compliance was monitored through individual monthly activity records (Appendix M) in which daily exercise was recorded. Space was provided for the date, number of sets, repetitions, and weight lifted. These activity records were mailed in by the exercise subjects on a monthly basis. Subjects were contacted by phone and regular home visits were arranged to review the exercise protocol, discuss any problems, ensure safety in lifting technique, check the appropriateness of weight used, and, if necessary, to provide monthly activity forms.

Two specific warm-up routines were provided to all subjects, however, they could use their own program if they preferred. A warm-up period was defined as a time during which body temperature and heart rate were increased, and allowed for "limbering-up". A warm-up could therefore include doing household chores or garden work. Two specific warm-up programs that were used by majority of the subjects were calisthenics and a power-walking program (Appendix N).

Subjects were asked to continue with their normal lifestyle habits, and no restrictions were placed upon other activities.

2.11. *Hormone Replacement Therapy*

The hormone replacement regime consisted of either estrogen alone (hysterectomized women) or estrogen in combination with progestogen. The route of estrogen administration was either oral or transdermal; the particular dose and route of administration was determined by the subject in consultation with her personal physician thus the regimes varied greatly. HRT was oral estrogen as conjugated estrogen, Premarin™ (Ayerst Laboratories), Estraderm™ (estradiol-17β, CIBA-Geigy Canada Ltd.), and Provera™, (medroxyprogesterone acetate, UpJohn Company of Canada). The doses and regimes are outlined in Table 2.2.

Table 2.2 Hormone replacement therapy: doses & regime

DOSES	REGIMES
Premarin™ (conjugated estrogen)	Day 1 to 21 (cyclic)
0.3 mg	Day 1 to 28 (continuous)
0.625 mg	
Estraderm™ (estradiol 17β)	Day 1 to 21 (cyclic)
25 ug	Day 1 to 28 (continuous)
50 ug	
100 ug	
Provera™ (medroxyprogesterone acetate)	Day 1 to 14
5 mg	Day 14 to 25
10 mg	Day 13 to 25
	Day 16 to 25

2.12. *Data Analysis*

Data analysis included both descriptive and inferential statistics; drop-outs were not included in the analysis. The level of significance for all comparisons was $\alpha = 0.05$, with power $(1-\beta)$ of 0.80.

The entire study population, and each separate study group was characterized at baseline using descriptive statistics, (i.e. mean, standard deviation) for age, years since

menopause, anthropometrics, fitness parameters, dietary intake, and measured bone mass variables. The amount and type of physical activity was provided in the form of both descriptive analysis and frequency distributions.

Analysis of variance (ANOVA), *t*-test, correlation, and stepwise regression were employed in data analysis.

A factorial ANOVA was first applied to baseline data for control, transfer control and treatment groups to ensure they were drawn from the same population. Subsequently, the control and transfer control groups will be combined as one "control" group if they are found to be from the same population.

A single factor ANOVA with repeated measures was used to test the difference between the sample means. The single-factor was made up of three levels (i.e. the study groups): (1) control, (2) exercise, and (3) hormone replacement. The dependent variables were measurements of bone mass, anthropometrics, fitness parameters, biochemistry, and nutrient intake. Reproductive and calciotrophic hormones were to be analyzed only at the study end-point. The Scheffé post hoc test was used for comparison among the means. In the preliminary data analysis for groups with less than three measurement periods the *t*-test was used rather than ANOVA.

The rate of bone mass change at each site (distal radius, proximal femur, lumbar spine) was calculated as a percentage. Pearson product-moment correlation was used to determine the magnitude and direction of relationship between the rate of bone change between the different sites, in other words to determine if bone mass at different skeletal sites (i.e. radius, femur, spine) changes at the same or different rates (dependent variable).

Stepwise regression was used to identify the optimal set of predictor variables for bone mass. The independent variables were anthropometrics, fitness parameters, biochemistry, nutrient intake, and physical activity level.

Two statistical programs, StatView™ SE + Graphics (1988) and SuperANOVA™ (1989) (Abacus Concepts Inc.), run on a Macintosh computer, were used for study analysis.

2.12.1. Data Editing

If any data points appeared anomalous based on either the mean of the study population (i.e. greater than four standard deviations above the mean) and/or existing empirical data, this data was not used in the analysis. An explanation has been provided in the results when any data values have been eliminated as a result of experimental error.

Chapter 3: Results

This study had been underway for approximately 18 months when interim data analysis was performed. However, the majority of subjects (n = 46/50) had not yet completed their 18-month measurement period. Individual subject starting time, and therefore measurement periods, varied greatly as recruitment was continued up to one year after initiation of the study. The maximum number of measurements for any one variable in this analysis is three which includes: 0-month (or baseline), 6-month, and 12-month measurement periods.

Fifty five women originally entered into the study and 50 remained at the time of this preliminary analysis. Five women dropped out of the study: one control subject, one exercise subject, and 3 HRT subjects. Reasons given for not continuing participation were radiation exposure, medical, personal, time commitments, and discontinuation of HRT. Six subjects who were unable to remain with their original assigned study group but wished to continue in the study were placed into a "Transfer Control" group. For example, three subjects allocated to the exercise group were unable to place the weight-training equipment in their apartments (due to lack of space) were reassigned to the transfer control group. Further details of the transfer control group and explanations for subject drop-out are outline in Appendix O.

The majority of the exercise group subjects entered the study within 6 months of its initiation. However, since the weight-training program was delayed approximately one year (due to design and manufacturing problems with the equipment) it had only been underway for about 6 months at the time of interim data analysis. Ten of the exercise subjects were therefore considered as "controls" during the period that they were actively involved in the study but not receiving treatment (i.e. the period including the 0- and 6-month measurement). With the addition of the exercise subjects (n = 10), and the

transfer controls (n = 6), the control group had thirty-one subjects for analysis from baseline to the 6-month measurement period; change in TBD at the distal radius over the first 6 months was determined from this data.

Factors affecting the outcome of the study are discussed here to provide a clearer understanding of the results, and their limitations. At the beginning of the study, due to the number of study measurements for each subject and the lack of study manpower, collection of anthropometrics (i.e. skinfolds & girths only) and strength data were not routinely obtained, however, all subjects have at least one measurement period which includes these variables. Fourteen of fifty subjects (14/50) had anthropometrics and strength measurements completed at baseline, 6/50 at the 6-month period, and 30/50 at 12 months.

The DER equipment became available in January 1989 about 12 months after study initiation. Subjects who entered at the beginning of the study (i.e. February 1988) had their first DER measurement at the 12-month point.

No subjects were excluded from the study as a result of rapid bone loss, or dropped out due to acute injury caused by the exercise program. One subject, however, attributed tendonitis in one elbow to the exercise program and was unable to continue exercises with that arm for approximately 4 months.

3.1 Baseline Data

3.1.1 Physical Characteristics

At the beginning of the study, groups did not differ statistically in age (54.0 ±2.2 years; mean ±SD) age at menopause (51.2 ±2.0 years), years since menopause (2.8 ±1.4 years), height (162.9 ±5.3 cm), weight (65.5 ±9.2 kg), BMI (24.7 ±3.4 kg m^{-2}), absolute VO_2max (1.27 ±.2 ml kg^{-1}), strength (Table 3.1), skinfolds, and girths (Table 3.2).

Subjects from the transfer control group were added to the regular control group as no significant differences were found between these groups.

Comparing all three study groups the HRT subjects were found to be slightly taller and heavier. Being slightly larger it was not surprising that subjects in the HRT group showed greater absolute strength in their arms and legs, although this was not significantly different from other groups.

Three control subjects, 3 exercise subjects, and 7 HRT subjects had hysterectomies prior to the natural cessation of menstruation; all had at least one intact ovary. Six of the study participants were cigarette smokers, and 19/50 had smoked at sometime in their life prior to the study.

Maximal oxygen uptake was not measured at the time of other baseline measurements (i.e. individual subject starting time). For the control and HRT subjects VO_2max was measured after 3.2 and 4.1 months into the study, respectively; for exercise subjects VO_2max was measured at an average of 5.1 months prior to the commencement of treatment. There were no significant differences between mean VO_2max values of the control, exercise, and HRT groups at baseline (20.2 ± 2.9 ml kg^{-1} min^{-1}, 20.1 ± 3.3 ml kg^{-1} min^{-1}, 19.3 ± 3.9 ml kg^{-1} min^{-1}, respectively). VO_2max values for two subjects were excluded due to instrumentation failure in data acquisition during the test.

Five skinfold sites and 7 girth sites were measured, and these data (with the exception of flexed arm) are shown in Table 3.2. No significant differences between study groups were detected for these variables. Sum of five skinfolds (SOS), and sum of trunk skinfolds (SOTS) were not significantly different between groups, although the HRT group had a higher value than the other two groups which was also reflected in weight and BMI. Waist to hip girth measurement ratio (WHR) values were similar for the control ($0.78 \pm .04$), exercise ($0.77 \pm .04$), and HRT groups ($0.79 \pm .06$). The flexed arm girth was not included in this analysis due to technical error.

Table 3.1 Physical characteristics of the study population and individual study groups at baseline

Parameter	Study Population (n = 50)		Control Group (n = 21)		Exercise Group (n = 12)		HRT Group (n = 17)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Age (years)	54.0	2.2	54.6	2.1	54.6	2.1	53.0	2.1
Age at menopause	51.2	2.0	51.3	1.9	51.9	1.2	50.8	2.5
Yrs since menopause	2.8	1.4	3.1	1.4	2.8	1.8	2.2	1.0
Body height (cm)	162.9	5.3	162.5	6.0	162.9	2.1	163.3	6.3
Percentile*	55.6		55.5		55.6		60.1	
Body weight (kg)	65.5	9.2	64.2	8.3	62.7	9.1	69.1	9.8
Percentile*	56.3		50.2		44.8		70.1	
BMI (kg m^{-2})	24.7	3.4	24.3	3.0	23.6	3.1	26.0	3.8
Percentile*	51.5		53.5		62		37.5	
VO_2max								
relative (ml $kg^{-1}min^{-1}$)	19.9	3.3	20.2	2.9	20.1	3.3	19.3	3.9
absolute (l min^{-1})	1.27	0.20	1.29	0.20	1.22	0.15	1.31	0.24
Leg strength, 1RM (kg)	89.8	23.6	82.6	22.3	96.3	30.0	93.7	18.0
Grip strength (kg)								
combined◊	54.7	7.6	53.7	7.8	51.3	5.9	58.1	7.4
Percentile*	44		40		25.8		60.5	

◊ combined = right and left grip strength are combined

* Percentile = based on the normative data prepared by Fitness Canada, Canadian Standardized Test of Fitness (1987)

Table 3.2 Skinfold and girth measurements of study population and individual study groups at baseline

Parameter	Study Population (n = 50)		Control Group (n = 21)		Exercise Group (n = 12)		HRT Group (n = 17)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Skinfold (mm)								
Triceps	20.9	5.2	21.4	4.5	20.7	6.0	20.3	5.6
Biceps	10.3	4.4	10.4	3.5	10.9	5.7	9.8	4.6
Subscapular	17.1	6.1	16.1	4.7	16.5	5.0	18.5	7.9
Iliac crest	15.2	6.3	13.8	5.2	16.1	7.1	16.4	7.1
Medial calf	17.5	5.1	17.8	5.2	18.8	6.1	16.2	4.2
SOS†	80.6	21.3	79.1	18.3	81.0	23.0	82.1	24.7
Percentile*	55.7		58.2		55		53.2	
SOTS†	32.2	11.2	29.6	9.0	32.6	11.5	34.8	13.2
Percentile*	52		62		51		45.5	
Girth (cm)								
Relaxed arm	29.7	2.8	29.4	2.6	29.0	2.9	30.4	2.9
Chest	89.3	5.6	88.9	4.5	88.6	6.6	90.3	6.3
Waist	79.1	8.4	78.0	7.9	78.0	7.1	81.1	9.8
Hip	101.8	7.5	100.5	7.5	101.9	7.0	103.3	7.9
Thigh	58.8	4.7	58.7	4.2	57.4	6.3	60.1	3.8
Calf	36.2	2.7	35.9	3.3	35.8	2.2	36.9	2.2
WHR†	0.78	0.05	0.78	0.04	0.77	0.04	0.79	0.06
Percentile*	50		50		57.5		45	

† measurement names are defined under abbreviations

* Percentile = based on the normative data prepared by Fitness Canada, Canadian Standardized Test of Fitness (1987)

3.1.2 Bone Mass Measurements

Table 3.3 shows baseline bone mass measurements for the distal radius, proximal femur, Ward's triangle and lumbar spine. BMD of the lumbar spine (1.004 ± 0.106 g cm^{-2}, $p < 0.01$), and Ward's triangle (0.624 ± 0.099 g cm^{-2}, $p < 0.01$) for the HRT group were statistically significantly different from the control (0.896 ± 0.119 g cm^{-2},0.536 ± 0.82 g cm^{-2}, respectively), and exercise groups (0.899 ± 0.70 g cm^{-2},0.524 ± 0.100 g cm^{-2}, respectively), at baseline.

As noted earlier DER measurements are not truly pre-treatment baseline values as the equipment did not become available until 12 months after the study had started. The first measurement using this equipment was made at an average of 7 months after

treatment started for both control and HRT groups, and approximately 1.5 months prior to treatment for the exercise group.

There was a tendency for the HRT group to have a larger bone mass at all measurement sites compared with the control and exercise groups.

Table 3.3 Bone mass measurements for study population and individual study groups at baseline

Parameter	Study Population (n = 50)		Control Group (n = 21)		Exercise Group (n = 12)		HRT Group (n = 17)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
γ-CT (g cm^{-3})								
Distal radius	0.280	0.057	0.278	0.064	0.267	0.051	0.291	0.054
DER (g cm^{-2})								
Proximal femur	0.880	0.122	0.871	0.085	0.850	0.130	0.913	0.152
Wards triangle	0.560	0.100	0.536	0.082	0.524	0.100	**0.624**	0.099
Lumbar spine	0.932	0.115	0.896	0.119	0.899	0.070	**1.004**	0.106

bold = significantly different from other study groups ($p < 0.05$)

3.1.3 Physical Activity Level

The assignment of participants to one of three activity categories; sedentary, moderately active or active, was based on the evaluation of present activity habits using the Physical Activity Questionnaire at baseline. Due to difficulty in summarizing and categorizing historical data on physical activity, it has not been included in this analysis. The distribution of subjects by present physical activity level is shown in Table 3.4. Forty-six percent of all women were considered to be "active", 40% moderately active and 14% sedentary. The exercise group had no subjects categorized as sedentary.

Table 3.4 Subject distribution by physical activity level at baseline

Study Group	Sedentary	Moderately Active	Active	Total
Control group	4	7	10	21
Exercise group	0	6	6	12
HRT group	3	7	7	17
Total	7	20	23	50

3.1.4 Nutrient Intake

Tables 3.5, 3.6, 3.7, and 3.8 shows mean, standard deviation, minimum, maximum and percentage of the recommended nutrient intake for Canadians (RNI) for 23 nutrients, energy, and number of food records completed, in the study population, control, exercise and HRT groups, respectively. Dietary intake for the three groups did not differ significantly for any of the nutrients measured.

The calcium intake from food alone averaged 873 ±351 mg day^{-1} for the study population at baseline. At entry into the study, individual daily calcium intake varied greatly from 344 to 1572 mg. Table 3.9 shows the distribution of subjects at various dietary calcium intakes; 28/50 subjects fell into one of two ranges: (a) 500 to 699 mg, (b) 900 to 1099 mg of calcium per day. The exercise group had a greater average calcium intake (1019 ±366 mg day^{-1}), but this was not significantly different from control (823±320 mg day^{-1}) or HRT groups (827±352 mg day^{-1}). At baseline 7/12 exercise, 4/21 control, and 6/17 HRT group subjects had dietary calcium intakes over 1000 mg day^{-1}.

Table 3.5 Dietary intake of the study population at baseline

Nutrient	Study Population (n = 50)				
	Mean	(SD)	Minimum	Maximum	Mean % RNI
Energy (Kcal)	1702	(457)	770	3188	91
Energy (kJ)	7118	(1913)	3223	13337	91
Calcium* (mg)	873	(351)	180	1815	109
Protein (g)	78	(24)	31	176	164
Carbohydrate (g)	203	(57)	82	352	—
Fat (g)	65	(29)	13	155	—
Vitamin A (IU)	9904	(12032)	554	73734	248
Niacin (mg)	19.0	(7.6)	4.9	45.2	126
Thiamin (mg)	1.4	(0.6)	0.4	4.3	161
Riboflavin (mg)	1.8	(0.6)	0.7	6.1	169
Vitamin B6 (mg)	1.6	(0.6)	0.4	3.4	136
Vitamin B12 (mcg)	4.1	(5.7)	0.3	63.7	203
Folacin (mcg)	215	(79)	82	559	111
Vitamin C (mg)	124	(71)	2	348	275
Vitamin D (IU)	206	(163)	0	923	206
Vitamin E (mg)	7.4	(8.1)	0.1	59.8	123
Iron (mg)	12.3	(4.3)	5.4	32.1	176
Magnesium (mg)	308	(99)	125	722	141
Zinc (mg)	10.6	(4.4)	3.7	28.6	133
Phosphorus (mg)	1320	(441)	592	3468	165
Dietary fibre (g)	16	(8)	4	59	—
Saturated Fat (g)	23	(12)	4	71	—
PUFA (g)	11	(7)	.8	39	—
Cholesterol (mg)	290	(178)	19	812	—
Sodium (mg)	2462	(1282)	533	9605	427
Potassium (mg)	3031	(804)	1205	5886	157
Number of food records	49		—	—	—

* Calcium = dietary calcium only, this does not include supplemental calcium

Table 3.6 Dietary intake of the control group at baseline

Nutrient	Control Group (n = 21)				
	Mean	(SD)	Minimum	Maximum	Mean % RNI
Energy (Kcal)	1694	(448)	940	2972	92
Energy (kJ)	7081	(1873)	3929	12432	92
Calcium* (mg)	823	(320)	212	1815	103
Protein (g)	74	(20)	37	133	156
Carbohydrate (g)	206	(61)	88	332	—
Fat (g)	64	(29)	16	134	—
Vitamin A (IU)	8230	(8646)	1496	44615	206
Niacin (mg)	17.9	(7.1)	5.5	40.3	119
Thiamin (mg)	1.2	(0.4)	0.6	2.5	143
Riboflavin (mg)	1.6	(0.5)	0.7	2.8	154
Vitamin B6 (mg)	1.4	(0.5)	0.4	3.3	129
Vitamin B12 (mcg)	3.4	(2.6)	0.3	12.7	170
Folacin (mcg)	212	(78)	82	422	111
Vitamin C (mg)	140	(73)	29	348	310
Vitamin D (IU)	210	(144)	0.1	657	210
Vitamin E (mg)	8.0	(9.8)	0.1	59.8	133
Iron (mg)	11.5	(3.7)	5.6	22.8	165
Magnesium (mg)	285	(76)	125	534	131
Zinc (mg)	9.7	(4.2)	3.7	28.0	121
Phosphorus (mg)	1207	(316)	592	2154	151
Dietary fibre (g)	15	(5)	4	33	—
Saturated Fat (g)	21	(11)	4	55	—
PUFA (g)	12	(9)	2	39	—
Cholesterol (mg)	284	(188)	19	742	—
Sodium (mg)	2325	(945)	807	5534	410
Potassium (mg)	2881	(671)	1549	4455	152
Number of food records	20		—	—	—

* Calcium = dietary calcium only, this does not include supplemental calcium

Table 3.7 Dietary intake of the exercise group at baseline

Nutrient	Exercise Group (n = 12)				
	Mean	(SD)	Minimum	Maximum	Mean % RNI
Energy (Kcal)	1750	(497)	910	3188	98
Energy (kJ)	7320	(2080)	3797	13337	98
Calcium* (mg)	1019	(366)	323	1749	127
Protein (g)	88	(28)	31	176	193
Carbohydrate (g)	197	(61)	82	352	—
Fat (g)	69	(27)	19	127	—
Vitamin A (IU)	12113	(15001)	929	73734	303
Niacin (mg)	19.4	(7.6)	4.9	45.2	127
Thiamin (mg)	1.5	(0.7)	0.5	3.8	174
Riboflavin (mg)	2.0	(0.9)	1.0	6.1	193
Vitamin B6 (mg)	1.6	(0.5)	0.6	3.2	128
Vitamin B12 (mcg)	5.4	(10.2)	1.1	63.7	271
Folacin (mcg)	239	(99)	98	559	127
Vitamin C (mg)	124	(73)	2	298	276
Vitamin D (IU)	215	(148)	0.1	733	215
Vitamin E (mg)	6.7	(6.7)	2.0	33.1	111
Iron (mg)	13.5	(5.2)	6.0	32.1	193
Magnesium (mg)	337	(123)	135	698	161
Zinc (mg)	12.0	(4.3)	6.0	28.6	150
Phosphorus (mg)	1500	(471)	699	2670	188
Dietary fibre (g)	19	(8)	4	53	—
Saturated Fat (g)	27	(12)	5	53	—
PUFA (g)	11	(7)	3	31	—
Cholesterol (mg)	295	(174)	60	797	—
Sodium (mg)	2519	(1504)	877	9605	458
Potassium (mg)	3285	(1030)	1205	5886	178
Number of food records	12		—	—	—

* Calcium = dietary calcium only, this does not include supplemental calcium

Table 3.8 Dietary intake of the HRT group at baseline

Nutrient	HRT Group (n = 17)				
	Mean	(SD)	Minimum	Maximum	Mean % RNI
Energy (Kcal)	1678	(445)	770	2559	86
Energy (kJ)	7017	(1863)	3223	10702	85
Calcium* (mg)	827	(352)	180	1805	103
Protein (g)	77	(25)	36	144	153
Carbohydrate (g)	203	(49)	118	328	—
Fat (g)	63	(31)	13	155	—
Vitamin A (IU)	10316	(13037)	554	49137	258
Niacin (mg)	19.9	(8.0)	9.9	43.5	133.
Thiamin (mg)	1.5	(0.7)	0.4	4.3	174
Riboflavin (mg)	1.8	(0.6)	0.8	3.3	169
Vitamin B6 (mg)	1.7	(0.6)	0.6	3.4	150
Vitamin B12 (mcg)	3.9	(3.6)	0.7	22.4	193
Folacin (mcg)	202	(67)	90	376	100
Vitamin C (mg)	104	(62)	17	315	232
Vitamin D (IU)	196	(194)	0.0	923	196
Vitamin E (mg)	7.1	(6.8)	0.8	36.1	118
Iron (mg)	12.4	(4.1)	5.4	30.0	177
Magnesium (mg)	314	(98)	198	722	138
Zinc (mg)	10.7	(4)	4.8	25.6	133
Phosphorus (mg)	1327	(505)	660	3468.3	166
Dietary fibre (g)	17	(9)	4	59	—
Saturated Fat (g)	22	(14)	4	71	—
PUFA (g)	10	(6)	0.8	26.7	—
Cholesterol (mg)	293	(174)	41	812	—
Sodium (mg)	2582	(1459)	533	6802	425
Potassium (mg)	3029	(738)	1735	5630	150
Number of food records	17		—	—	—

* Calcium = dietary calcium only, this does not include supplemental calcium

Table 3.9 Subject distribution by dietary calcium intake at baseline based on 3-day food records.

Study Group	Dietary Calcium intake (mg) 300-499	500-699	700-899	900-1099	1100-1299	>1300-1500	Total
Control group	2	6	4	6	2	0	20
Exercise group	0	3	1	3	2	3	12
HRT group	2	5	3	5	1	1	17
Total	4	14	8	14	5	4	49

With calcium supplementation mean daily calcium intake was increased to 1468 ±200 mg. The average calcium intake for each group before and after supplementation is shown in Table 3.10. The majority of subjects, 23/50, were supplemented with 500 mg calcium per day, with 11/50, 7/50, 5/50, and 4/50 receiving 1000 mg, 750 mg, 250 mg and no supplement, respectively.

Analysis of the nutrition questionnaire and the diet history will be made at the study end-point and no interim data is available.

Table 3.10 Average calcium intake before and after supplementation

Study Group	Average Calcium intake (mg) Before Supplementation		After Supplementation	
	Mean	(SD)	Mean	(SD)
Control Group	823	(320)	1456	(213)
Exercise Group	1019	(366)	1453	(228)
HRT Group	827	(352	1494	(175)
Average	873	(351)	1469	(201)

3.1.5 Clinical Laboratory Data

Nineteen biochemical variables were measured (refer to Table 3.11) and three of these were significantly different between groups at baseline. Ionized calcium was significantly higher in the control group (1.33 ±0.05 mmol L^{-1}, $p < 0.01$) as compared to the exercise (1.29 ±0.04 mmol L^{-1}) and HRT groups (1.29 ±0.02 mmol L^{-1}). Lactate dehydrogenase (LD) was significantly lower in the HRT group (128.94 ±25 IU L^{-1}, $p < 0.01$) compared to the control (147.33 ±17.47 IU L^{-1}) and exercise group (148.58 ±14.22 IU L^{-1}). The HRT group had four LD values less than 111 IU L^{-1} whereas the other two groups had no values below 119 IU L^{-1}. Serum protein was significantly different between the exercise group (68.08 ±3.32 g L^{-1}) and the HRT group (71.47 ±2.6 g L^{-1}, $p < 0.05$).

3.1.6 Analysis of Baseline Data

Using all the study variables at baseline, except the nutrients but including calcium, a correlation matrix was calculated. Based upon the results of variables used in a prediction equation of a stepwise regression, correlation values between -0.45 and 0.45 from the correlation matrix table were not included in the following discussion. With this criterion, TBD in the distal radius at baseline was not correlated with any other variable. Lumbar spine BMD was correlated with leg strength ($r = 0.510$). Proximal femur BMD was correlated with Ward's triangle BMD ($r = 0.921$), weight ($r = 0.466$), BMI ($r = 0.501$), relative VO_2max ($r = -0.577$), calf skinfold ($r = 0.593$), thigh and calf girth measurement ($r = 0.448$ & 0.595, respectively). Ward's triangle BMD was positively correlated with proximal femur BMD ($r = 0.921$) weight ($r = 0.536$), calf skinfold ($r = 0.582$), thigh and calf girth measurement ($r = 0.598$ & 0.688, respectively).

Using a stepwise regression model, baseline variables that were considered to be potential predictors of bone density were entered as independent variables with one of the three bone mass measurement as the dependent variable. The independent variables chosen were: age, years postmenopausal, height, weight, BMI, VO_2max, arm and leg strength, calcium intake, physical activity level, and the remaining bone mass measurements (i.e. those other than the dependent variable). Significant predictors of distal radius were found to be Ward's triangle BMD, physical activity level, and years since menopause. Combined in a prediction equation these variables would result in an r^2 of 0.235, with a standard error of estimate (SEE) of 0.050. Only one predictor was determined for the lumbar spine BMD — the proximal femur BMD with $r^2 = 0.234$, and SEE = 0.101. The proximal femur BMD was found to have the greatest number of predictors and the greatest r^2 value of 0.429 with SEE = 0.094. In order of significance the predictors were: Ward's triangle BMD, lumbar spine BMD, weight, and height ($p < .05$). Ward's triangle BMD had three predictors, only two of which were significant; proximal femur BMD and age ($r^2 = 0.382$, and SEE = 0.081).

3.2 Changes Over Time

3.2.1 Physical Characteristics

Over an average of 11 months, the exercise group increased slightly in weight (1.6%); weight for the HRT group decreased slightly (-0.88%), and that for the control group was unchanged (0.06%), however, these changes were not statistically significant. A change of 1.5% in BMI from 23.6 kg m^{-2} to 24.0 kg m^{-2} was considered significant ($p < 0.05$) in the exercise group, no significant changes were found in the other two groups. Height changes were not significantly different between the groups.

At the time of the 12-month VO_2max test the exercise group (n = 11) had completed an average of 5.2 months of exercise, whereas the control and HRT groups

had 14.6 and 12.5 months of "treatment", respectively. There were no significant differences in the VO_2max results between study groups.

The exercise group had completed two measurement periods for strength (arm & leg) and anthropometrics over 6 months of weight-training. However, from the control and HRT groups only 8 and 7 subjects, respectively, had completed their second strength and anthropometric measurements. In the exercise group combined grip strength increased from 51.3 ±5.9 kg to 53.8 ±4.5 kg, and leg strength increased from 95.3 ±30 kg to 97.2 ±24.7 kg, although neither change was significant. Of the 5 skinfold and 7 girth measurements taken in the exercise group, only the hip girth changed significantly over 6 months, decreasing from 101.9 ±7.0 cm to 100 ±6.8 cm ($p < 0.05$)

3.2.2 *Bone Mass Measurements*

The percentage changes in bone mass at the distal radius, proximal femur, and lumbar spine in the study groups are shown in Table 3.12.

Distal radius: The increase in trabecular bone mass from baseline seen in the control group was not significant at either the 6- or 12-month period, 0.35% and 0.20%, respectively. TBD was above baseline by an average of 0.63% in the 12 women who had exercised for an average of 5.2 months. This change, however, from 0.267 ±0.052 g cm^{-3} to 0.268 ±0.052 g cm^{-3} was not statistically significant. The HRT group showed the greatest change in TBD (+1.47%), after 12 months of treatment, this increase was significantly different from both baseline and the 6-month measurement ($p < 0.01$).

Proximal femur: For the control and HRT groups the baseline measurement was taken 7 months after treatment was initiated, however, over a 6-month period the control group showed a 0.46% decrease in bone mineral density in the femur, and the HRT

group showed a non-significant increase (0.29%). Treatment duration in the exercise group averaged 5.7 months at the time of the second measurement, when subjects showed an average increase of 0.43%.

Ward's triangle: TBD data at this site was found to be inconsistent in all groups due to technical difficulties with this new procedure. Large differences (up to 51%) were seen over the 6-month period, and therefore this data was not used in the analysis.

Lumbar spine: Both control and exercise groups showed decreases in BMD at the lumbar spine, -0.71% and -0.83%, respectively; the HRT group showed a small increase, 0.14%, but none of these changes were significant.

Table 3.12 Percent change in bone mass across two time periods for each study group

Parameter	Control Group % difference		Exercise Group % difference	HRT Group % difference	
	0-6 mo (n = 31)*	0-12 mo (n = 19)	0-6 mo (n = 12)	0-6 mo (n = 16)	0-12 mo (n = 16)
γ-CT					
Distal radius	0.35	0.20	0.63	0.19	1.47
	0-6 mo (n = 18)		0-6 mo (n = 12)	0-6 mo (n = 14)	
DER					
Proximal femur	-0.46		0.43	0.29	
Lumbar spine	-0.71		-0.83	0.14	

* 10 of the exercise subjects were included as controls as the exercise program was delayed for 6 months

3.2.3 Exercise Program

Table 3.13 provides data for individual subjects in the exercise group. Using the leg exercise apparatus, subjects were lifting approximately 93% of body weight; the amount varied between 44% to 167% body weight. The amount of weight lifted with the arms averaged 3.3 kg.

The distal radius was measured after an average of 5.6 months (range 3 to 9) of exercise. Eight of twelve subjects exercising showed non-significant increases in TBD at the distal radius.

Lumbar spine and proximal femur bone mass measurements were made after an average of 6.1 months (range 4 to 9) of exercise. Five subjects showed a slight increase in BMD at the spine, and 7 subjects an increase in BMD at the femur, however, none of these values were significantly different from baseline. These results suggest that the mechanical load placed on the bones of the femur with the exercise used is greater than for the spine. One subject (#9) appeared to be losing bone rapidly at the spine (-6.05%) even though she was lifting 104% of her body weight using her legs; this loss was unexplained.

At this time no relationship is seen between bone mass changes and the amount of weight lifted in either the legs or arms. The number of months exercised also does not appear to influence bone mass, however, 6 months may be too early in the exercise program to measure change on an individual basis.

Compliance with the weight-training program was 85% which was assessed through the monthly activity forms kept by the subjects. Each subject was expected to exercise 20 days per month, or approximately 5 times per week, to achieve 100% compliance.

Table 3.13 Average number of months exercised, weight lifted and percent change in bone mass in individual subjects in the exercise group

SUBJECT	NO OF MONTHS EXERCISED		WEIGHT LIFTED*		PERCENT CHANGE IN BONE MASS		
	γ-CT (months)	DER	LEGS (% body wt)	ARMS (kg)	RADIUS	SPINE	FEMUR
1	5	5	65	3	-0.22	-1.24	-0.83
2	9	9	167	5.1	-0.62	1.49	0.96
3	5	9	101	4.1	1.19	-1.64	-0.70
4	8	8	44	3.2	2.57	0.64	-2.47
5	4	4	59	2.5	-0.04	2.26	0.19
6	3	6	100	3	1.14	2.31	0.25
7	4	6	97	4.1	0.64	-2.59	2.25
8	4	6	81	2	1.27	-1.54	2.99
9	5	5	106	3	2.45	-6.05	-1.25
10	4	5	113	3.8	0.95	1.18	0.46
11	8	4	78	2.6	-3.26	-2.75	-0.73
12	8	7	96	2.8	1.47	-2.04	4.07
Average	5.58	6.17	93	3.3	0.628	-0.831	0.433

* Average amount weight lifted for the arms & legs, based on number of "DER" months exercised.

3.2.4 Physical Activity Level

Forty-six subjects completed a one-year physical activity questionnaire. Activity level over the year was found to change significantly ($p < 0.01$) for the study population. The distribution of subjects at baseline is compared to that at 1 year in Table 3.14. The activity level of the exercise and HRT groups changed significantly ($p < 0.05$), while that for the control group did not. At baseline half (6/12) of the exercise group was categorized as moderately active and the other half as active, however, after one year 9/11 were categorized as active and only 2/11 as moderately active, primarily due to the involvement in the weight-training program (11/12 subjects had completed the 1-year physical activity questionnaire). The HRT group decreased from 3 subjects who were originally in the sedentary category to 0, and increased from 7 to 12 subjects in the active group.

Table 3.14 Subject distribution by physical activity level at baseline

Study Group	Sedentary		Moderately Active		Active		Total	
	baseline	1-year	baseline	1-year	baseline	1-year	baseline	1-year
Control group	4	3	7	8	10	8	21	19
Exercise group	0	0	6	2	6	9	12	11
HRT group	3	0	7	4	7	12	17	16
Total	7	3	20	14	23	29	50	46

3.2.5 Nutrient Intake

Three-day food records were obtained every six months. Forty-eight of fifty subjects completed the first food record, 45/50 completed the second, and at the time of this interim analysis, 43/50 of the third food records had been completed and analyzed using the nutrient database. A repeated measures ANOVA was made for the three study groups over the three measurement periods (baseline, 6 and 12-month food records). Of the 26 variables analyzed only saturated fat was found to be significantly higher in the exercise group at baseline (26.68 ±8.15 g) compared to the 6-month value (18.19 ±3.01 g).

Although the subjects' diets were all supplemented with calcium to 1500 mg day^{-1}, the food records still analyzed only dietary calcium. Within each group dietary calcium varied minimally for food record #1, #2, and #3, and is shown in Table 3.15

Table 3.15 Mean daily dietary calcium intake based on 3 food records for the 3 study groups

Food Record Number	Control Group Mean (SD)	Exercise Group Mean (SD)	HRT Group Mean (SD)
#1, calcium (mg day^{-1})	804 (242)	1019 (316)	814 (308)
#2, calcium (mg day^{-1})	795 (301)	967 (349)	912 (310)
#3, calcium (mg day^{-1})	869 (313)	1056 (197)	774 (218)

3.2.6 Clinical Laboratory Data

Three measurement periods have been included in the analysis of biochemical data, baseline, 6 and 12-month measurements. Forty-three of the subjects have completed the 12-month measurement period.

Albumin corrected total calcium, alkaline phosphatase, and AST where found to be significantly different in the study population over the three measurement periods (i.e. 12 months). Using ANOVA for the individual treatment groups alkaline phosphatase and AST were found to be significantly different in the control group ($p < 0.05$, $p < 0.01$, respectively); and AST in the exercise group ($p < 0.05$).

Chapter 4: Discussion

Postmenopausal osteoporosis is a multifactorial disease, however, estrogen deficiency has been implicated as one of the main causes of net bone resorption. HRT is therefore used as a primary form of intervention to reduce bone loss in postmenopausal women. Less is known about the influence of mechanical loading on the skeleton in this age group, however, exercise may also have an important therapeutic role in the reduction of bone loss. Exercise has been recommended to modulate or even reverse bone loss (Lanyon 1989; Dalsky 1987; Schapira 1988; Aloia 1981). Bone strength is highly correlated with bone mass, therefore, if bone mass could be held constant, through exercise for example, one would predict a reduction in the occurrence of spontaneous (i.e. bone fragility) hip fractures in later years resulting from osteopenia. Thus the question arises — is a specific form of weight-training an effective method to maintain bone mass, and is it a viable therapeutic alternative to HRT in postmenopausal women?

After 6 months of weight-training the exercise group showed a trend to increased TBD and BMD at the distal radius and proximal femur, respectively, however none of these bone mass changes were significant, concurrently vertebral BMD was slightly decreased (not significant; ns). Over a 6-month training period maximal oxygen consumption, and arm and leg strengths did not change significantly, although average physical activity level within the group did increase significantly, primarily due to the addition of the weight-training program. Significant changes in anthropometric measurements were an increase in BMI, and a decrease in hip girth. Compliance with the exercise program over an average of 6 months was high. Using the leg press apparatus the subjects lifted an average of 93% of their body weight, and used an average hand weight of 3.3 kg for their arm exercises, after approximately 6 months of training.

After 12 months of hormone replacement therapy the HRT group showed a significant increase in TBD at the distal radius. No change was observed in BMD at the proximal femur or lumbar spine in this group after 6 months of HRT, however, the first

bone mass measurements using DER were not made until approximately 7 months after treatment was initiated. No change was observed in maximal oxygen consumption after 12 months of therapy, however during this time physical activity level had increased significantly from baseline.

Although the control group received 1500 mg calcium per day, no significant changes were observed in bone mass over 12 months, however, there was a trend towards a non-significant decrease in BMD at the lumbar spine during this time. Maximal oxygen consumption, and physical activity level did not change significantly over the 12-month period.

Significant predictors of distal radius TBD were Ward's triangle BMD, physical activity level, and years since menopause. The proximal femur BMD could be predicted from Ward's triangle BMD, lumbar spine BMD, weight and height; while lumbar spine BMD could be predicted by proximal femur BMD and age.

4.1 Exercise Effect on the Skeleton

A number of prospective exercise intervention studies (Aloia et al., 1978; Smith et al., 1981; Krølner et al., 1983; White et al., 1984; Dalsky et al., 1988; Chow et al., 1987) support the concept that exercise maintains bone mass in older women. However, closer examination of these studies reveals a number of methodological problems which may have resulted in unreliable data. In general, due to the heterogeneity of these reported studies, they can not be directly compared (e.g. different bone mass measurement techniques were used). The reported changes in bone mass were not usually significant relative to the precision of the equipment used. For example, using DER and commercial whole body CT, the required annual change in bone mass that must occur is 2% and 12%, respectively, for significance at the 95% confidence level. Major shortcomings of previous studies are: non-randomization of subjects; allowing subjects to receive concomitant HRT, type of exercise used, and short duration of study .

We observed a trend (ns) to increased TBD at the distal radius after 6 months of specific weight-training, which agrees with data reported by Simkin et al. (1987), Smith et al. (1981) and White et al. (1984). This trend may indicate that an increase in trabecular bone mass is influenced by site-specific training in humans. Previous studies in athletes (Nilsson & Westlin, 1971; Jones et al., 1977; Huddleston et al., 1980) and in animals (Lanyon, 1984; Lanyon et al., 1986) support the concept of site-specific training, as they found that exercise has primarily a "local effect" upon that part of the skeleton stressed. This indicates that when an exercise program is designed specifically to increase bone mass, that a particular part of the skeleton must be stressed directly, and monitoring must also be specific to this site. By measuring TBD, which is more physiologically responsive due to its large surface area and high rate of metabolic activity relative to cortical bone, it was possibly easier to detect bone mass trends in our study.

We found no significant changes at the proximal femur or lumbar spine after 6 months of exercise training, a result which agrees with Rockwell et al. (1989) whose study had only a 4 month duration. However, we did see a slight trend towards increased BMD at the proximal femur which may indicate that the amount of weight, and the type and intensity of exercise performed, may have placed a more optimal stress on the femur. Both the work of Rockwell et al. and of our group were limited by the short study duration. When one considers that the length of a remodeling cycle is approximately 3 months 9 months of training is probably more appropriate to detect a "true" change in bone mass.

There are several possible explanations for why we observed no significant changes in bone mass at the sites measured after approximately 6-months of exercise intervention. First, the changes may have been small relative to the sensitivity of our present methods of measurement. We needed to observe a change of 2% to be significant ($p < 0.05$). Second, individual seasonal variation in bone mass may be greater than changes from the exercise intervention (Bergstralh et al., 1989). Third, the necessary

peak strain rate in the particular bones measured may not have been attained with the exercise prescription used. Fourth, relative to the length of a bone remodeling cycle for the exercise duration to this time may have been too short.

It is also thought that there may be a certain "threshold" level of activity before changes occur. This threshold may be different for each individual, and might also depend on an individuals baseline activity. For example, individuals who are already active may not show an increase in bone mass as readily as an individual classified as sedentary. In our study the exercise threshold for the lumbar spine may not have been reached, thus resulting in no change or a slight decrease in bone mass at this site.

Although not reaching levels of significance our preliminary results show a trend which suggests that a specific weight-training program with the frequency, intensity, and duration used, may inhibit bone loss from the distal radius and proximal femur in postmenopausal women. The change observed in the distal radius, where only TBD is measured, is larger than that in the proximal femur BMD where integral bone was measured. With only 6 months of exercise data we cannot reach a conclusion concerning the efficacy of our particular exercise prescription, however, the trends in this data do support a beneficial effect of exercise on the skeleton and we must await the study end-point to confirm these findings.

4.2 *Physical Activity Level and its Relationship to Bone Mass*

Quantification of habitual physical activity is most frequently obtained through questionnaire. Since postmenopausal bone mass depends upon both peak bone mass reached during the mid-thirties, and cumulative bone loss after that time, physical activity level should be assessed over a lifetime (i.e. including both past and present activity patterns). Three studies have been reported and all concluded that physical activity level made an important contribution to bone mass in women (Stillman et al., 1986, Kriska et al., 1988, Halioua & Anderson 1989). In our study only "present" physical activity

level (previous 12 months) was analyzed, and we found no significant difference in bone density at the distal radius, lumbar spine, or proximal femur in women who were categorized as "active" relative to those who were classified as "sedentary". From previously reported studies it is noted that the wider the age range (e.g. Stillman et al. whose subjects ranged from 30 to 85 years old) the stronger the relationship between physical activity and bone mass. This most likely results from the fact that younger women generally have greater bone mass and are more active than older women. Three particular factors limited our study in detecting a relationship between physical activity level and bone mass: first, the age range of our study population was only 7 years (50 to 57); second, historical physical activity level may have more influence on bone mass than present activity level, or a combination of both, and third, the validity of our physical activity assessment instrument needs to be established.

Maximal oxygen uptake (VO_2max) is generally accepted as a good index of aerobic work capacity or fitness level, but genetic factors are also important. Using predicted maximal oxygen uptake Pocock et al. (1986) found bone mass and VO_2max significantly, and independently correlated with age. In contrast to this work a recent report by Tobin et al. (1989) found that VO_2max (maximal treadmill test) was not an independent predictor of BMD. Our data agrees with the findings of Tobin et al. We found no correlation between VO_2max and bone mass, although we were limited by our study age-range (i.e. 50 to 57 years), and the small variation in VO_2max values within the study population. However, it is unlikely that the stimulus for bone accretion is the same as that needed to increase aerobic capacity. Aerobic activity leads to greater cardiovascular endurance and increases muscular strength in muscles specific to the activity. The influence of VO_2max on the skeleton observed by Pocock et al. (1986) is probably a spurious correlation. The increasing bone density observed with increasing VO_2max is most likely due to mechanical stress developed by the activity rather than with cardiovascular training per se. This means, in general, that people with high VO_2max

levels will not always have significantly greater bone density compared with age matched control subjects. Swimmers, for examples, may have a high VO_2max while their bone density is considered only average.

The mean VO_2max value that we obtained by direct maximal testing using the bicycle ergometer was slightly lower than that found by other researchers who measured VO_2max in postmenopausal women (Chow et al., 1987; Smith et al., 1989; Dalsky et al., 1988). According to the CSTF our subjects were slightly heavier and taller than age-matched controls, which resulted in an lower relative VO_2max. Treadmills are often used for exercise testing, however, it has been reported to overestimate VO_2max by 5 to 10% compared with the bicycle ergometer (Åstrand et al., 1973). Often VO_2max is obtained by indirect methods, through submaximal testing, which provides values within ±10% of those obtained by direct methods.

Maximal oxygen consumption in our study groups did not change over one year of study. Since the exercise used was not aerobically based this result was not surprising. It was anticipated, however, that with their new found strength from the weight-lifting program, the exercise subjects might become more active, and this would be reflected in the VO_2max test. Improvements in VO_2max have been observed after 12 months of aerobic exercise (Chow et al., 1987).

4.3 Muscle Strength and the Skeleton

With knowledge of the relationship between mechanical stress in bone and bone hypertrophy it has been postulated that muscular strength is correlated with bone density (Sandler 1989; Sinaki & Offord 1988; Bevier et al., 1989; Pocock et al., 1989). Sandler (1988) suggested that normative data, based on age, sex, and body habitus, be determined for muscular strength to assess the adequacy of mechanical loading. This could in turn be used for preliminary screening of bone strength in a quick, inexpensive fashion such as at a regular medical check-up. Testing for muscular strength using

traditional methods (i.e. determining one repetition maximum using free weights with bench or leg press) is not feasible for the general population. Several studies have examined predictors of bone mass and muscle mass, and strength in the upper limb, and have found a positive relationship between grip strength and forearm bone density (Bevier et al., 1989; Sandler et al., 1989; Pocock et al., 1989). We did not find a significant correlation between grip strength and TBD at the distal radius. This result may have been due to the limited range in age (i.e. 50 to 57 years) and/or the size of our sample (n = 50). Therefore, implementing a simple handgrip strength test as part of an annual check-up might not be adequate to distinguish between the bone density of women in the high risk age category of 50 to 60 years. Using a Cybex isokinetic dynamometer Pocock et al. (1989) found quadriceps strength to be a predictor of femoral neck bone mass. Sinaki and Offord (1988) found bone density of the lumbar spine in 68 healthy postmenopausal women to be significantly correlated with back extensor strength. This data suggests that a relationship exists between strength of a specific muscle group and the corresponding bone. We measured leg strength using a specially designed leg-press apparatus, but we had difficulty in using this equipment to accurately and precisely determine maximum repetition in individual subjects. With specialized equipment, such as the Cybex isokinetic dynamometer, leg strength determination would be easier and the data obtained more accurate and reliable, however, the use of such an instrument was not practical for this study.

4.4 Hormone Replacement Effects on the Skeleton

Munk-Jensen et al. (1988) and Ettinger et al. (1987) found that HRT inhibited bone loss at the distal radius after one year of treatment, and our study gives a similar result with a significant increase in TBD from baseline at this site.

Using dual photon absorptiometry (DPA) increases in BMD have been reported in the lumbar spine after HRT compared with annual losses of 2% in controls (Ettinger,

1986). We were unable to detect any significant change in bone mass at either the lumbar spine or proximal femur over a 6-month period using DER, a method with significantly better precision and sensitivity than DPA. At the time of the first DER measurement, however, subjects had been receiving HRT for only an average of 7 months (range from 0 to 19 months). Potentially, the HRT therapy should have influenced the outcome, particularly if bone hypertrophy occurs primarily during the initial months of therapy. However, it is difficult to precisely monitor change over a 6-month period in a small group of subjects (n = 17) in which an average change of about 2% from baseline is anticipated over 2 years.

4.5 Calcium Effects on the Skeleton

The increase in the TBD at the distal radius in the HRT group may have been influenced to some degree by the increased availability of calcium through supplementation. Although diet in all the subjects contained approximately the same amount of calcium, a synergistic effect between calcium and HRT has been reported (Ettinger et al., 1987). When 1500 mg per day of calcium was provided, estrogen dosage could be reduced by half and still retain its effectiveness in preventing bone loss. Also, estrogen has been reported to increase calcium bioavailability (Lindsay, 1987). The influence of calcium per se may not lead to reduced loss of bone (i.e. "more" protection), but rather may only allow the quantity of estrogen to be reduced, indicating that the effects of calcium and estrogen on the skeleton are not additive.

Calcium supplementation to the diet of healthy postmenopausal women has been thoroughly studied (Nilas, 1984; Riggs et al., 1986; Riis et al., 1987; Recker et al., 1977). The amount of daily calcium intake our subjects were consuming has not been reported to have any significant effect on bone mass in healthy postmenopausal women.

Over 40% of postmenopausal women in Canada do not meet the RNI for calcium (Shah & Belonge, 1988). In our study the baseline calcium level was assessed for each

subject by means of a 3-day food record and a calcium assessment form. The mean calcium intake was greater than the RNI for Canadians (800 mg). In general, women who volunteer for research studies come from a higher socio-economic class, have a higher education level, and are usually informed about health issues. These factors may strongly influence food choices. Thus, in our study it is not surprising to find the average calcium intake to be high. However, it is interesting to note that over 40% of our subjects still had calcium intakes less than the RNI.

4.6 *Study Compliance*

Compliance in our study was excellent, over the 6-month period of exercise only 1/12 of the exercise subjects dropped out. This can be compared with other exercise and bone research studies in which 28% of exercise subjects dropped out in 6-months (White et al., 1984). Our high compliance rate in the exercise group was probably due to the convenience of in-home exercise facilities, the regular contact with subjects (i.e. by phone and home visits) and the individual feedback provided.

4.7 *Significance of this Work*

This thesis presents the first research to date that compares the effects of a specific weight-training exercise program with the effects of HRT on bone mass in healthy postmenopausal women. Previous exercise intervention studies have involved very general forms of physical activity (i.e. aerobics, general fitness classes) from which it is difficult to delineate the particular activity affecting bone mass. In our study, however, a very specific and carefully designed weight-training program for the upper and lower limbs was used. However, with only 6 months of exercise data analyzed, we are unable to draw any conclusions concerning either amount or intensity of weight-training required to beneficially impact on bone mass in postmenopausal women or on relative efficacies of exercise and HRT. The trends in our data suggest, however, that physical activity might

be effective as an inhibitor of bone loss in the postmenopausal years, and we must await completion of the entire study to confirm this expectation. This pilot trial has been very successful to date, with a low drop-out rate, and high subject compliance. This study is also the most comprehensive undertaken with respect to exercise effects upon the skeleton. Additionally, the measurement of bone mass provides the most precise data available. We are therefore confident that the bone mass changes seen at the distal radius, lumbar spine and proximal femur are valid and reflect the true effects of the treatments. If weight-training exercise should be shown to inhibit local bone loss with an efficacy similar to that of hormone replacement then a non-pharmacological therapy could be offered to postmenopausal women for the maintenance of bone mass and hence prevention of future osteoporosis. It could also lead to a specific exercise prescription for women with respect to the type, amount, intensity, and duration of weight-training required to achieve a retention in bone mass. Our exercise program was conceived on the premise that by applying different loads (strain) to bone, and varying the number of repetitions and strain rate, bone mass would increase as previously shown in animals (Lanyon 1984), thus, this research is the first to specifically apply exercise principles developed in animal models to humans.

4.8 Future Applications

At the end of the 2 year clinical trial, if expectations for the exercise program are realized, then such programs will not only provide an alternative to those women who are presently using HRT to maintain bone mass, but also provide a form of therapy for high risk individuals who are unable to use HRT, or for those who dislike the idea of taking "pills" and "medication". It will facilitate the preparation of specific exercise prescriptions using similar resistance and loading principles as used in weight-training, and apply these principles to other forms of exercise (e.g. tubing, body resistance, etc.). Exercise programs and prescriptions may also be applicable to premenopausal women, and

particularly to those found to be genetically at "high risk" for osteoporosis. Athletes prone to stress fractures, may also require a specific "bone-building" exercise. However, many questions remain unanswered, e.g.: "Does physical activity affect both age-related and the estrogen deficiency phase of bone loss similarly?" and "How do trabecular and cortical bone respond differently to mechanical stress?" Answers to these questions await the design and execution of future studies.

4.9 Conclusions

The purpose of this 2 year pilot clinical trial was to determine the effects of a specific weight-training exercise prescription on bone mass in healthy postmenopausal women, and compare this with the effects of hormone replacement therapy on bone mass.

Six and 12 month interim data were analyzed in this report. After the exercise group completed 6 months of a weight-training program specifically designed to load the distal radius, proximal femur and lumbar spine, no significant changes were observed in bone mass over this time, however, some trends were seen. Both trabecular bone density in the distal radius and bone mineral density in the proximal femur showed a tendency to increase. More data is required, however, before conclusions can be drawn about the efficacy of this particular weight-training program with respect to frequency, intensity and duration. However, the trend to increase in bone mass at these sites is encouraging, and more data may provide more definitive results. No change in BMD was observed in the lumbar spine, a finding due perhaps to not adequately, or specifically loading the vertebral column. The study end-point holds important information for the exercise program as this data will clarify the effect this weight-training program has on bone mass.

After 12 months of hormone replacement therapy, the HRT group was found to have significantly increased trabecular bone density at the distal radius. Hormone replacement therapy is a well established method for reducing the rate of bone loss in healthy postmenopausal women, therefore this finding was not unexpected. However,

no significant changes were observed in bone mineral density at the proximal femur and lumbar spine after only 6 months of treatment. For the HRT group more data will further establish the role of hormone replacement therapy. This data will also facilitate the determination of the influence of HRT at different sites in the body.

No change was observed in TBD in the distal radius in the study control group which received calcium only (1500 mg day^{-1}) for 12 months. BMD of the proximal femur and lumbar spine were not shown to change significantly after 6 months for the control group.

In our study population no relationship was observed between bone mass and maximal oxygen consumption, physical activity level, leg or arm strengths.

No firm conclusions can be drawn from this interim data analysis concerning the effects of weight-training on bone mass in postmenopausal women or its effects relative to HRT. Therefore, it is with some anticipation that we await the analysis of the 2-year study.

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APPENDIX A

Study Information Sheet

UNIVERSITY OF ALBERTA
Department of Applied Sciences in Medicine

INFORMATION SHEET

TITLE: **A pilot study to document the efficacies of hormone replacement and of controlled weight-training exercise in preventing menopause-related bone loss**

INVESTIGATORS: Dr. T.R. Overton
Dr. D.C. Cumming
Ms. C.L. Viger

The purpose of this 24 month study is to gain a better understanding of the biological processes which lead to skeletal problems, particularly in the postmenopausal female population between the ages of 50 to 57 years when an accelerated rate of bone loss may occur. The primary aim of this research is to compare the relative efficacies of hormone replacement and of weight-training exercise in reducing the rate of postmenopausal bone loss.

This research group has developed new methods for measuring bone density. The gamma-ray (γCT), and x-ray (XCT) computed tomography systems measure bone density by passing a very narrow beam of radiation through different bones in the body. Then, by measuring the amount of radiation transmitted, we can determine the density of bone at different sites. The radiation exposure for these bone measurements is less than 100 millirads to each small measurement area, and no biological effect has been demonstrated from exposure to this quantity of radiation to the forearm (distal radius) or lower limbs (distal tibia). For measurements of the hip (proximal femur) and spine (lumbar vertebrae) using the newly available method of dual energy radiography (DER) the radiation exposures to these sites will less than 5 mR.

Pre-assessment of your health status will be necessary. This usually includes a medical history and physical examination done by a medical doctor, blood and urine biochemical analyses, x-rays of spine as necessary and a fitness assessment. Two x-rays will be taken, one AP thoraco-lumbar spine and one lateral view of the same area. Radiation exposure from these routine medical x-rays is about 500 mR per film. A dietary assessment will determine the amount of calcium supplementation each participant will require. Any volunteer demonstrating a health problem will be referred for appropriate medical follow-up, and those who appear to be at risk to their health will not be accepted into the study.

On entry into the study, you will be randomly assigned to 1 of 2 experimental groups, namely:

1) calcium supplementation group;
2) calcium supplementation plus weight-training group.

Subjects will be allocated to the hormone replacement group since they already will be receiving therapy. The choice for hormone replacement will be determined solely by the patient and her physician.

Participants in the exercise group will engage in a structured, weight-training program in their own home.

Your health status will be carefully monitored during your participation in the study by a number of blood and urine biochemical analyses, by bone densitometry of your wrist, leg (lower tibia and hip) and lumbar spine, and by fitness monitoring with treadmill and cardio-respiratory function tests.

The risks to you by participating in this study are outlined in the **consent to participate** form. For those subjects on hormone replacement the drug risks are listed and include even the remotest side effects that have been described. The estrogen dose used in this study is the lowest strength available (the maximum recommended therapeutic dose can be 8 times higher), and the progesterone is given to counteract the risks of estrogen replacement.

Your participation in this study will be greatly appreciated. However, you should be aware that you may choose to withdraw at any time without explanation or prejudice to future follow-up for skeletal investigation. We ask you to sign the **informed consent** to participate in the study. We would urge you to ask about any part of the study which you do not understand, at any time during your participation. Any travel expenses incurred in attending the study related visits will be reimbursed, and all medication required for the study will be provided to you free of charge. Information obtained from participation in this study may be published in medical reports but participant's identities will be kept confidential.

Persons who can be contacted about this research:

Dr. T.R. Overton 432-6339
Ms. Shirley McFadyen (research coordinator) 432-6340
Ms. Cindy Viger (research assistant) 432-6339

Appendix A

APPENDIX B

Informed Consent

UNIVERSITY OF ALBERTA
Department of Applied Sciences in Medicine

CONSENT TO PARTICIPATE IN A STUDY

TITLE: A pilot study to document the efficacies of hormone replacement and of controlled weight-training exercise in preventing menopause-related bone loss

1. I agree to participate in a 24-month research project which involves random assignment of participants to different study groups, to determine if calcium supplementation with or without a controlled weight-training exercise program can prevent the rapid bone loss that has been documented for women at the time of menopause.

2. I understand that I may receive an oral calcium supplement to provide me with a maximum of 1500 mg daily as determined by a dietary assessment.

3. I authorize Dr. Cumming and/or assistants as may be selected by them to perform the following procedures on myself:

   a) Medical history and physical examination.
   b) Any screening/diagnostic procedures that are, in Dr. Cumming's or their designate's professional judgement, necessary and desirable in determining the status of my health.
   c) Baseline and subsequent blood and urine tests for biochemical analyses as necessary for the purpose of the study. Blood taken will not exceed 250 ml in any 6 month period
   d) A total of 6 measurements of bone density will be made for the distal radius (forearm) and distal femur, proximal tibia (knee region). If new instrumentation becomes available for spine and hip studies a maximum of 6 studies will also be made for these regions.
   e) Baseline and subsequent electrocardiograms (ECG's) as necessary.
   f) Baseline x-rays of thoraco-lumbar spine (AP and lateral).

4. I authorize Dr. C.T. Kappagoda and/or his assistants to administer baseline and subsequent fitness evaluations every 12 months to include:

   a) Anthropometric measurements including height, weight, skinfold and girth measurements.
   b) Bicycle ergometer test, which involves riding a stationary bicycle for approximately 20 minutes while the workload is increased. While this test is being performed your oxygen consumption, blood pressure, cardiac output and ECG (12 lead electrocardiogram) will be monitored.
   c) Muscular strength of the arms and legs will be determined.

5. I understand that I may discontinue any of these tests at any time. If any indications of abnormal response to these tests become apparent to supervisory staff, I understand that the test will be discontinued immediately.

6. If I am allocated to the weight-training group, I understand that I will be required to perform a daily, 5-10 minute weight-lifting exercise program in my home, using a simple, safe apparatus provided to me for the duration of the study and installed at no personal cost.

7. Dr. Cumming or their designate has explained the purpose of the study to me, and I understand the necessity for the several study visits and the procedures outlined in this consent form.

8. It is possible that one or more of the following risks or discomforts may occur during some of the procedures:
   a) The placement of a needle in an arm vein to draw blood may cause slight discomfort and possibly a bruise at the site of the puncture.
   b) The measurement of bone density in the research involves a yearly radiation exposure of less than 100 millirads to the small areas measured; the baseline x-rays involve a radiation exposure of 1000 millirads to the abdomen. No biological effect has been demonstrated from exposure to these quantities of radiation.
   c) Some generalized muscle and joint discomfort may occur initially as a result of the exercise program.
   d) Fitness testing may cause some shortness of breath with or without some mild chest discomfort.

9. I understand that there will be no cost to me for study related visits, doctor's fees or required medication during my participation in the study.

10. I understand that I will be informed of any significant findings which may develop during the research period that may affect my willingness to continue participating in the study.

11. I understand that the information obtained from my participation in this study may be published in medical reports, but that my identity will be kept confidential.

12. I understand that copies of the study information sheet and the signed consent form will be given to me.

13. The study described here has been explained to me and I understand the inherent risks and benefits, and I voluntarily consent to participate in it. I have read this form and I have had the opportunity to ask questions which have been answered to my satisfaction. I understand that I may refuse to participate, or may withdraw from the study at anytime without explanation or prejudice to my future medical care.

_____	_____
Subject name (print)	Subject signature and date
Witness name (print)	Witness signature and date

Appendix B

UNIVERSITY OF ALBERTA
Department of Applied Sciences in Medicine

CONSENT TO PARTICIPATE IN A STUDY

TITLE: A pilot study to document the efficacies of hormone replacement and of controlled weight-training exercise in preventing menopause-related bone loss

1. I agree to participate in a 24-month research project to determine if hormone replacement along with calcium supplementation can prevent the rapid bone loss that has been documented for women at the time of menopause.

2. I understand that I may receive an oral calcium supplement to provide me with a maximum of 1500 mg daily as determined by a dietary assessment, and that I will continue to receive conjugated estrogen (eg. Premarin™ or Estraderm™ daily for 25 days each calendar month, and medroxyprogesterone acetate (Provera™) 10 mg daily for 10 days each calendar month as previously agreed with my personal physician.

   It is possible that I may experience one or more of the following side effects as explained to me by my personal physician or by Dr. Cumming or his designate. Possible risks and side effects of estrogens which have been described include the following:

   a) Vaginal breakthrough bleeding, spotting, withdrawal bleeding, or overgrowth and malignant change of the lining of the uterus. However, the simultaneous administration of medroxyprogesterone will control the bleeding and reduce the chance of cancerous change of the uterus to that for women not receiving estrogen.
   b) Fibroids in the uterus may enlarge and endometriosis may become active, but withdrawal of the drug will reverse these changes if they occur.
   c) Increased blood clotting may occur, but this is rare with the dose and type of estrogen used in this study. Enhanced risks occur in individuals who are relatively immobile, smoke , have heart or malignant disease, or have other injury, recent surgery or infection .
   d) Nausea and vomiting may occur but this is uncommon with the dose and type of estrogen used in this study.
   e) Breast discomfort may occur in about 1 in eight women receiving the hormone.
   f) Fluid retention and/or weight gain may occur rarely, but such changes are significant only in patients with heart trouble.
   g) High blood pressure may develop or be increased with estrogen treatment; this is unusual with the dosage preparation of estrogen used in this study, and will return to normal if the treatment is discontinued.
   h) Mildly abnormal changes in blood sugar control may occur, but there is no evidence that estrogens induce diabetes mellitus.
   i) Women taking estrogen for long periods of time are approximately 2.5 times more likely to develop gall bladder disease.
   j) Rare allergic reactions have caused skin rashes.

   Possible risks and side effects of medroxyprogesterone acetate (Provera™) which have been described include:

   a) Skin rashes, increased blood clotting, nausea, nervousness, insomnia, sleepiness, fatigue, dizziness and depression have been reported rarely.
   b) Fluid retention of a minor degree may occur more commonly.

c) It may cause some withdrawal bleeding in some women during the week off medication.

3. I understand that the particular hormone replacement therapy that I receive will be a decision determined by myself, and by my personal physician in consultation with the project clinical staff, and that it will be my doctor's responsibility to discuss with me all risks and benefits, and to provide me with my own prescription for medication. For subjects enrolled in the study these prescriptions will be filled at no charge.

4. I authorize Dr. Cumming and/or assistants as may be selected by him to perform the following procedures on myself:

   a) Medical history and physical examination.
   b) Any screening/diagnostic procedures that are, in Dr. Cumming's or their designate's professional judgement, necessary and desirable in determining the status of my health.
   c) Baseline and subsequent blood and urine tests for biochemical analyses as necessary for the purpose of the study. Blood taken will not exceed 250 ml in any 6 month period
   d) A total of 6 measurements of bone density will be made for the distal radius (forearm) and distal femur, proximal tibia (knee region). If new instrumentation becomes available for spine and hip studies a maximum of 6 studies will also be made for these regions.
   e) Baseline and subsequent electrocardiograms (ECG's) as necessary.
   f) Baseline x-rays of thoraco-lumbar spine (AP and lateral).

5. Dr. Cumming or his designate has explained the purpose of the study to me, and I understand the necessity for the several study visits and the procedures outlined in this consent form.

6. It is possible that one or more of the following risks or discomforts may occur during some of the procedures:

   a) The placement of a needle in an arm vein to draw blood may cause slight discomfort and possibly a bruise at the site of the puncture.
   b) The measurement of bone density in the research involves a yearly radiation exposure of less than 100 millirads to the small areas measured; the baseline x-rays involve a radiation exposure of 1000 millirads to the abdomen. No biological effect has been demonstrated from exposure to these quantities of radiation.

7. I understand that there will be no cost to me for study related visits, doctor's fees or required medication during my participation in the study.

8. I understand that I will be informed of any significant findings which may develop during the research period that may affect my willingness to continue participating in the study.

9. I understand that the information obtained from my participation in this study may be published in medical reports, but that my identity will be kept confidential.

10. I understand that copies of the study information sheet and the signed consent form will be given to me.

11. The study described here has been explained to me and I understand the inherent risks and benefits, and I voluntarily consent to participate in it. I have read this form and I have had the opportunity to ask questions which have been answered to my satisfaction. I understand that I may refuse to participate, or may withdraw from the study at anytime without explanation or prejudice to my future medical care.

Appendix B

12. I authorize Dr. C.T. Kappagoda and/or his assistants to administer baseline and subsequent fitness evaluations every 12 months to include:

    a) Anthropometric measurements including height, weight, skinfold and girth measurements.
    b) Bicycle ergometer test, which involves riding a stationary bicycle for approximately 20 minutes while the workload is increased. While this test is being performed your oxygen consumption, blood pressure, cardiac output and ECG (12 lead electrocardiogram) will be monitored.
    c) Muscular strength of the arms and legs will be determined.

Subject name (print)	Subject signature and date
Witness name (print)	Witness signature and date

Appendix B

APPENDIX C ----------

Admission Criteria

UNIVERSITY OF ALBERTA
Department of Applied Sciences in Medicine

ADMISSION CRITERIA FOR RESEARCH STUDY

A pilot study to document the efficacies of hormone replacement and of controlled weight-training exercise in preventing menopause-related bone loss

****

Subject Name_____ **Subject Study Number** _____

	Yes	No
1. Is the female subject 50-57 years old or has she had surgical menopause?	[ ]	[ ]*
2. Is the subject willing to participate in the study as evidenced by the signing of an informed consent, and able to attend the laboratory at the specified study intervals?	[ ]*	[ ]
3. Has the subject been menopausal for at least one year but not more than 5 years, or has she had surgical menopause?	[ ]*	[ ]
4. Is the Clinical PI satisfied that there is no physical condition present which would prevent the subject from completing the study?	[ ]*	[ ]
5. Will the subject stop taking multivitamins and/or mineral supplements during the course of the study?	[ ]*	[ ]
6. Does this subject have any indication of skeletal disease as determined by history, physical examination, or laboratory test result?	[ ]	[ ]*
7. Does the subject have any history of malignant disease (except those localized to the skin)?	[ ]	[ ]*

	Yes	No
8. Does the subject have rheumatoid arthritis or other arthritic processes which may restrict mobility?	[ ]	[ ]*
9. Does the subject have active gastrointestinal or hyperacidity disease, or has had excisional surgery of the stomach or small bowel likely to produce malabsorption?	[ ]	[ ]*
10. Is the subject taking any diuretic therapy other than Lasix™(furosemide)?	[ ]	[ ]*
11. Does the subject have an active liver disease?	[ ]	[ ]*
12. Does the subject have a documented history of alcoholism?	[ ]	[ ]*
13. Does the subject have any condition that required treatment with steroids, androgens, estrogens, calcium, calcitonin, or vitamin D for three months or longer within the past six months?	[ ]	[ ]*
14. Does the subject have any history of fluoride treatment other than dental applications?	[ ]	[ ]*
15. Does the subject have any history of treatment with diphosphonate compounds?	[ ]	[ ]*
16. Does the subject have clinically significant renal impairment?	[ ]	[ ]*
17. Does the subject have clinically unstable cardiac disease?	[ ]	[ ]*
18. Is the subject hypertensive?	[ ]	[ ]*
19. Does the subject have a family history of, or a predisposition to diabetes mellitus?	[ ]	[ ]*
20. Does the subject have uterine fibroids or a history of endometriosis?	[ ]	[ ]*

Appendix C

21. Does the subject have a history of classical migraines?	[ ]	[ ]*
22. Does the subject have ophthalmic vascular disease?	[ ]	[ ]*
23. Does the subject have a history of epilepsy?	[ ]	[ ]*
Does the subject have a history of asthma?	[ ]	[ ]*
24. Does the subject have a regular calcium intake of less than 300 mg per day as determined by nutritional assessment?	[ ]	[ ]*
25. Does the subject have a trabecular bone density of less than 0.125 g/cm^3 for the distal radius?	[ ]	[ ]*
26. Does the subject have at least 2 vertebra in the T12-L3 region that are structurally intact and without significant wedging as determined from measurements of lateral spine x-rays?	[ ]	[ ]*
27. Does the subject have evidence of osteoporosis as determined by1 or more vertebral compression fractures and radiographic evidence of demineralization of the vertebrae.	[ ]	[ ]*
28. Does the subject have indications of secondary causes of osteoporosis as determined by history, physical examination or laboratory tests?	[ ]	[ ]*
29. Does the subject have any other generalized diseases of bone such as hyper/hypoparathyroidism, Paget's disease, renal osteodystrophy, or other metabolic bone diseases?	[ ]	[ ]*

30. Does the subject have any known sensitivities or allergies to food or drugs? If yes, list. [ ] [ ]

In order to be eligible for entry into this study all responses marked with an asterisk must be checked. Any exceptions to these criteria must be approved by both the Clinical PI and the Study PI, and detailed below:

Name of person completing this form **Date**

Clinical PI **Study PI** **Date**

Appendix C

APPENDIX D

Diet History and Nutrition Questionnaire

NUTRITION QUESTIONNAIRE

DATE OF INTERVIEW _____

INTERVIEWER_____

SUBJECT'S NAME:_____

Read subjects file prior to interview for general infomation on age, occupation, height, weight, etc.

_____

_____

Record subjects **weight** from chart. _____

Record subjects **height** from chart. _____

1. Are you following a special diet at this time? If you are what kind of diet are you on?

_____

_____

_____

3. Are you taking vitamin and/or mineral supplements? If yes, please name the brand and the vitamins and/or minerals it contains as well as the dosage, if known.

_____

_____

_____

4. Are you taking any other food supplements? If yes, name the product and amount.

_____

_____

5. Are you allergic to any foods? If yes, please name these foods.

_____

_____

7. What do you think of your present weight? Do you consider yourself: underweight; at your normal weight; moderately overweight or very overweight?

_____

_____

8. Would you like to maintain your present weight, gain weight or lose weight at this time? If you would like to change your weight, what would you like to weigh?

_____

_____

9. What is the most you have ever weighed? At what age was this?

_____

_____

10. What is the least you have weighed in your adult life? At what age was this?

_____

_____

11. Are you planning in the near future to change your diet or eating habits in any way? If so why and how? (Please note that during the study period if you have altered your eating habits significantly please notify me as soon as possible so I can assess the adequacy of your diet.)

_____

_____

_____

12. Have you ever had an appetite problem. If so when and how long did it persist? Did you require medical treatment for it?

_____

_____

Appendix D

DIET HISTORY

1. Do you eat at regular times eat day? If no, why.
   _____

2. How many times a week do you eat:
   a) breakfast _____
   b) lunch _____
   c) dinner _____
   d) a meal in the late evening or night _____

3. How many times a week do you have a snack and what do you usually eat at these times? (morning, afternoon, evening, night)
   _____
   _____
   _____

4. Where do you usually eat and who do you eat with? (breakfast, lunch and supper)
   _____
   _____
   _____

5. Do you prepare your own meals? If no, who prepares the meals?
   _____
   _____

6. How often do you eat away from home?
   _____

7. What type of restaurants do you frequent (fast-food outlets, friends' homes, bag-lunches at work, restaurants)?
   _____
   _____
   _____

8. Do you have any food dislikes? What are they?
   _____
   _____

9. Are there any foods that you do not consume for any other reason? (eg indigestion)
   _____
   _____

10 Do you have any difficult chewing?
   _____
   _____

Appendix D

TYPICAL DAY OF EATING:

Weekday:

Weekend day:

Appendix D

APPENDIX E

Calcium Assessment Form

CALCIUM ASSESSMENT FORM

Subjects initials:	**Birthdate:**
Subject code:	**Date:**

FOOD TYPE	STANDARD SERVING SIZE	USUAL SERVING SIZE	FREQUENCY A DAY	B WK	C MO	D <MO	E NO	FREQ X SERV	MG CALCIUM /PORTION	MG CALCIUM /MONTH
1. Milk (any type)	250 ml								314	
2. Buttermilk	250 ml								300	
3. Chocolate milk	250 ml								300	
4. Ice cream	125 ml								92	
5. *Hard cheese	45 g								300	
6. Parmesan cheese	15 ml								69	
7. Cottage cheese	125 ml								151	
8. Plain yogurt	125 g								228	
9. Fruit yogurt	125 g								211	
10. Dried milk powder	15 ml								73	
11. Milkshake	250 ml								290	
12. Half & half (12%)	15 ml								16	
13. Coffee cream (18%)	15 ml								15	
14. Whipped cream	15 ml								4	
15. Sour cream	15 ml								17	
13. Cream cheese	15 ml								12	
14. Pudding	125 ml								178	
15. Custard	125 ml								157	
16. Rice pudding	125 ml								137	
17. Pr. cheese slices	1 slice								185	
18. Pr. cheese spread	15 ml								84	
18. ^Cnd sardines	7 med								367	
19. ^Cnd salmon	90 g								145	
20. Other fish	90 g								28	
21. Clams	7								46	
22. Other shellfish	90 g								61	
23. Chicken/Beef, etc	90 g								10	
24. Eggs	1 lg								26	
25. #Dried beans	250 ml								91	
26. Tofu	7x6x2								80	
27. Almonds	125 ml								200	
28. Brazil nuts	125 ml								130	
29. Other nuts	125 ml								50	
30. +Dark leafy greens	125 ml								90	
31. Broccoli	125 ml								94	
32. Mashed potatoes	250 ml								58	
33. Rhubarb	125 ml								184	
34. Fruit juice (any)	250 ml								26	
35. Bread	1 slice								23	
36. Pasta/rice	250 ml								16	
37. Pancakes/biscuits	each								46	
38. Macaroni & cheese	250 ml								382	

FOOD TYPE	STANDARD SERVING SIZE	USUAL SERVING SIZE	FREQUENCY A DAY	B WK	C MO	D <MO	E NO	FREQ X SERV	MG CALCIUM /PORTION	MG CALCIUM /MONTH
39. Chili-con-carne	250 ml								86	
41. Cheese pizza	1/8-35cm								144	
42. Cream soup, milk	250 ml								183	
43. Beer	341 ml								17	
44. Wine	100 ml								8	
44. "Coffee/tea	250 ml								7	
45. Chocolate bars	30 g								35	
46. Other:										
47. Other:										
48. Other:										
49. Other:										

Sum of monthly intake _____ - 30 = Daily intake _____ + 100 non-coded = Adjusted daily intake _____

Calculations:

* Hard cheese - cheddar, gouda, brick, mozzarella
^ Canned fish with the bones
# Dried beans - kidney, garbanzo, lima, navy, soy
+ Dark leafy greens - mustard greens, kale (cooked)
" Coffee/tea - based on the 1987 water analysis for calcium in Edmonton which was 28 mg/l

Calcium contents of foods taken from the Nutrient Values of Some Common Foods, 1987, which is based on the Canadian Nutrient File, Health Protection Branch, Health & Welfare Canada.

Appendix E

APPENDIX F ----------

3-Day Food Record

3 DAY FOOD RECORD

1988

FOR ADDITIONAL INFORMATION OR ASSISTANCE PLEASE CONTACT:

Shirley McFadyen at 432-6340
OR
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Principal Investigator

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Clinical Sciences Building
Room 10-105
University of Alberta
Edmonton, Alberta
T6G 2G3

Name: _____ **Date:** _____

Appendix F

Some HINTS for keeping your food record

(Please read through this information carefully prior to recording your food intake.)

1. First and foremost, DO NOT change your eating habits when keeping your food record. We DO NOT want you to record how you think you should be eating, rather how you usually eat. (For example, if you eat what you think is "too much" or the "wrong" type of food, please do not leave it off your food record, we rely on you to be as honest as possible.)

2. It is very important for you to record EVERYTHING that you eat and drink for the next 3-days in this booklet. Record two days during the week and one during the weekend.

3. To make recording easier for you, it is best to write down what you eat IMMEDIATELY after eating.

4. Fill out the record as complete as possible, remembering each category:

Some examples :

How much was eaten?

1 cup	of 2% milk
2 tsp	of margarine, soft, in tub
4 oz	of cottage cheese, 2%
30 grams	of canned salmon, sockeye in oil
2	small eggs
1-2"x 2"x 2"	iced brownie, with nuts

Description of food eaten

RAW	carrot sticks
BAKED	chicken with skin
CANNED	green peas, cooked in juice
FROZEN	strawberries, unsweetened (thawed)
BOILED	potato in skin
FRIED	small egg, fried with margarine

5. **Remember** these foods as they are commonly forgotten:

a) Between meal eating or snacks.
b) Gum, cough drops, antacids and candies.
c) Vitamin and mineral supplements.
d) Alcohol (wine, hard liquor, beer, etc.). It's important to be specific (eg. red or white wine, light or regular beer, percentage of alcohol).
e) Condiments, such as mustard and ketchup.
f) Additions to foods which includes things such as sugar, butter, sour cream, gravy, etc.

6. What do I do about recording **casseroles** and **mixed dishes?**

Foods such as homemade beef stew, chili con carne, tacos, chefs salad and even desserts (eg. cheese cake) can often be difficult to determine the exact proportions of ingredients that you have eaten. If you can accurately estimate everything in the food combination then please do so. Otherwise, if possible, write the **recipe** down in the space provided at the back of your food record booklet (blank pages are provided for **notes** or recipes) and record the size of portion you ate.

REMEMBER IF YOU HAVE ANY QUESTIONS - CALL !

Example of a food record:

DAY _____ DATE _____

Time of day	Amount	Description of Food

Appendix F

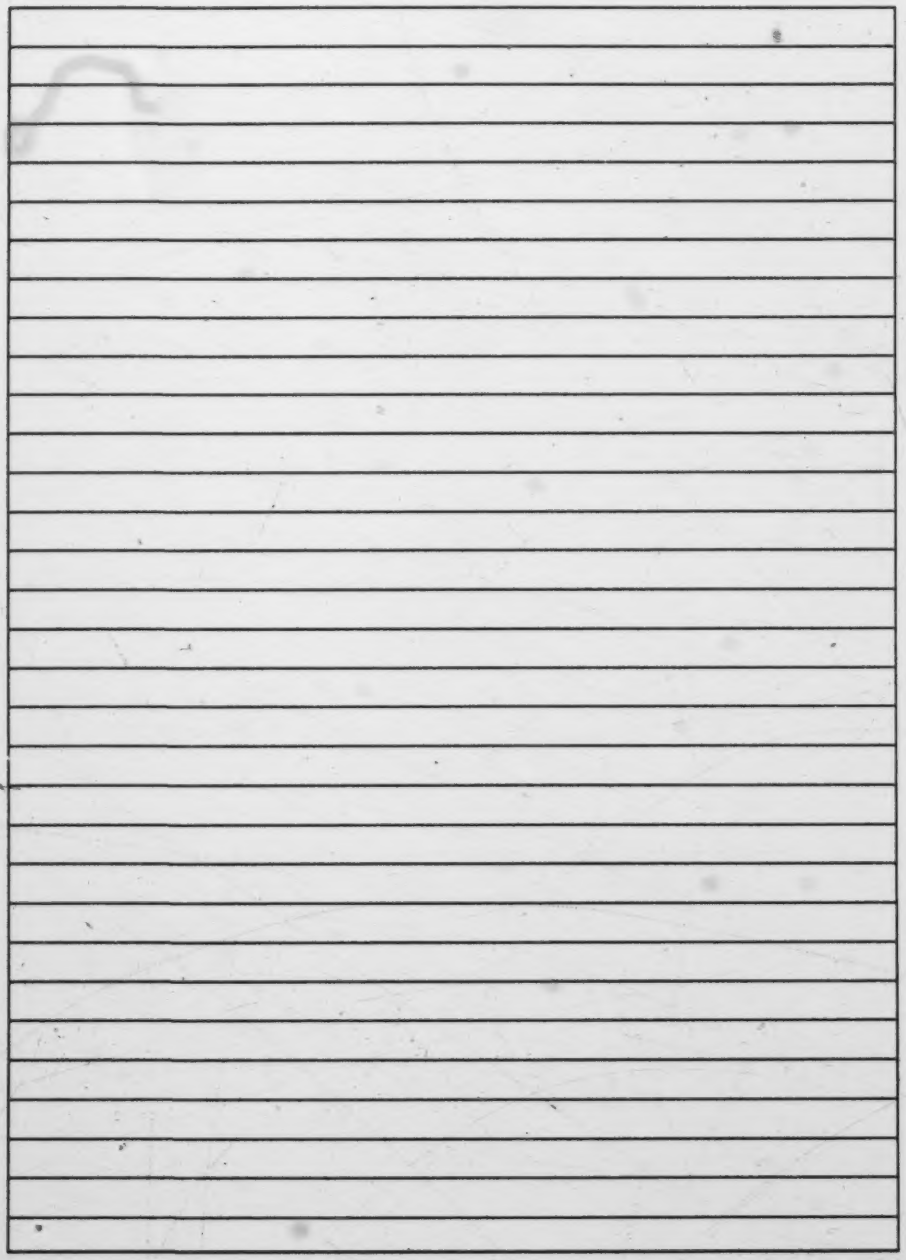
DAY _____ DATE _____

Time of day	Amount	Description of Food	

BONE RESEARCH UNIT FOOD RECORD

Appendix F

NOTES & RECIPES



Appendix F

APPENDIX G

Nutritional Database General Information

FACULTY OF DENTISTRY NUTRIENT DATA BASE

Nutrient Values in 100 G Edible

Portion of Foods Accessed by Weight

or in Common Portions

October 1989

7

/dbase1

DESCRIPTION OF THE NUTRIENT DATA BASE

Introduction and Sources of Data

The nutrient data base developed by the Faculty of Dentistry is based on the Kellogg Data Base. In 1985, it was updated with selected information from the 1985 Canadian Nutrient File (CNF, 1985), the United States Department of Agriculture handbooks (USDA, 1976-1984), Canadian food companies, and Pennington and Church's Food Values of Portions Commonly Used (Pennington and Church, 1985).

Between 1985 and 1987, selected nutrient values were added from the 1986 Canadian Nutrient file (CNF, 1986) and other published sources (HWC, 1979; 1985; Leveille et al., 1983; Paul and Southgate, 1978; Souci et al., 1981; USDA, 1986).

Between 1987 and 1989, additional foods and nutrient values were added from the 1988 Canadian Nutrient File (CNF, 1988) and other published sources (Lanza and Butrum, 1986; Matthews et al., 1987; Pennington et al., 1986, USDA, 1976-1987). Some of the nutrient values were imputed from recipes, according to procedures outlined by the United States Department of Agriculture (USDA, 1966).

Food Items

The nutrient data base consists of about 4200 foods which have been divided into 44 groups. They are listed in alphabetical order in Table 1 and as they appear on the computer screen in Table 2. The categories are based on food types, eg., Milk, Cream, Whipped Toppings or on common usage, eg. Desserts.

Within each food group, foods are listed in alphabetical order. For one food group, eg., Desserts: Cakes, Cookies, Pastries, Pies, Squares, the food group has been subdivided to aid in locating the food. Each food is in the data base only once, even though it could appear in more than one category.

Foods in the data base are in their ready-to-cook, ready-to-heat, or ready-to-eat form, as well as ingredient form. Brand names are used for foods for which the formulation was different from the generic form of the food or for which there did not exist a generic form. Manufacturer or brand names are at the end of a food name, separated from it by a hyphen.

Food names and descriptions are as complete as the information given in the source. Abbreviations are whenever possible, the same as those use in the Canadian Nutrient File. A complete list of abbreviations is shown in Table 3. Definitions of terms used are also listed in Table 3.

If a combination food is not available on the data base there are two choices for handling the situation. A substitute can be selected or the food can be treated as a recipe. An appropriate recipe is selected from a cookbook and entered onto the computer. The appropriate proportion or weight of the recipe is added to the subject's file. Adding the proportion can be an advantage when the subject knows only the proportion of the product consumed, eg., 1/7th of a pie or 1/5 of a casserole.

TABLE 1

Food Groups in the Nutrient data base*

No.	Food Group Name
2	Alcoholic Beverages
42	Baby Food
11	Bread, Rolls, Croutons, Stuffings
14	Breakfast Bars, Instant Breakfasts
36	Butter, Margarine, Oils, Fats
35	Candy, Gum
1	Carbonated Beverages
16	Cereals, Cooked
15	Cereals, RTE
8	Cheeses
3	Coffee, Coffee Substitutes
27	Combination Dishes
33	Desserts: Cakes, Cookies, Pastries, Pies, Squares
32	Desserts: Doughnuts, Danish Pastries, Sweet Rolls
34	Desserts: Ice Creams, Popsicles, Puddings, Sherberts, Jello
20	Eggs, Egg Dishes, Egg Substitutes
22	Fish, Seafood, Fish Analogs
41	Flours, Grains
19	French Toast
10	Fruit
9	Juices, Punches, Fruit-Flavoured Drinks
44	Legumes
21	Meat, Meat Analogs
6	Milk Drinks, Milk Drink Mixes
5	Milk, Cream, Whipped Toppings
12	Muffins, Biscuits, Dumplings, Loaves, Popovers
38	Non-Sweet Toppings, Condiments, Gravies, Salad Dressings
37	Nuts, Nut Butters, Seeds
17	Pancakes, Crepes
26	Pastas, Rice
24	Potatoes
23	Poultry
28	Salads, Jellied Salads
29	Sandwiches
31	Snacking Food, Crackers
30	Soups
43	Spices
39	Sweet Toppings, Spreads, Sugars, Syrups
4	Tea
13	Toaster Pastries
25	Vegetables
40	Vitamins, Minerals, Supplements
18	Waffles
7	Yogurt

* Food groups are listed on the computer screen in numerical order rather than alphabetical order, but the numbers do not appear on the screen.

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TABLE 2

Food Groups in the Nutrient Data Base
Listed as they Appear on the Computer Screen

Food Group Name
Carbonated Beverages
Alcoholic Beverages
Coffee, Coffee Substitutes
Tea
Milk, Cream, Whipped Toppings
Milk Drinks, Milk Drink Mixes
Yogurt
Cheeses
Juices, Punches, Fruit-flavored Drinks
Fruit
Bread, Rolls, Croutons, Stuffing
Muffins, Biscuits, Dumplings, Loaves, Popovers
Toaster Pastries
Breakfast Bars, Instant Breakfasts
Cereals, Ready to Eat
Cereals, Cooked
Pancakes, Crepes
Waffles
French Toast
Eggs, Egg Dishes, Egg Substitutes
Meat, Meat Analogs
Fish, Seafood, Fish Analogs
Poultry
Potatoes
Vegetables
Pastas, Rice
Combination Dishes
Salads, Jello
Sandwiches
Soups
Snacking Foods, Crackers
Desserts: Doughnuts, Danish Pastries, Sweet Rolls
Desserts: Cakes, Cookies, Pastries, Pies, Squares
Desserts: Ice Creams, Popsicles, Puddings, Sherberts
Candy, Gum
Butter, Margarine, Oils, Fats
Nuts, Nut Butters, Seeds
Non-Sweet Toppings, Condiments, Gravies, Salada Dressings
Sweet Toppings, Spreads, Sugars, Syrups
Vitamins, Minerals, Supplements
Flours, Grains
Baby Food
Spices
Legumes

Appendix G

TABLE 3

Abbreviations and Definitions Used in the Nutrient Data Base*

Abbreviations			
A	acid	MARG	margarine
ALC/VOL	alcohol by volume	MCG	microgram
APP	approximately	MED	medium
ARTIF	artificially	MF	milk fat
ASC	ascorbic acid (vitamin C)	mL	millilitre
		MOIST	moisture
BAT DIP	batter dipped	N	not/no
BBQ	barbecued	NFDM	nonfat dry milk
BR	breaded	NA	sodium
CASE	caseinate	NK	neck
CHOCO	chocolate	PKD	packed
CKD	cooked	PKG	package
CM	centimetre	PKT	packet
CND	canned	PPD	prepared
CONC	concentrate	PROT	protein
CTD	coated	RE	retinol equivalents
CTR	container	RED	reduced
CR	crumbled	REF	refuse
D	dark	REFRIG	refrigerated
DEC	declaration	RST	roasted
DIAM	diameter	R-T-C	ready-to-cook (oven ready)
DIL	diluted	R-T-S	ready-to-serve
DIP	dipped	SEP	separable
DM	diameter	SM	small
DRSTK	drumstick	SND	seasoned
EDIB	edible	SH	shredded
EN	enriched	SFT	sifted
ENVEL	envelope	SK	skin
EX	extra	SL	slice
FL	flesh	SOL	solids
FLR	flour	STABIL	stabilized
FRD	fried	SUB	substitute (as in egg substitute)
FRZ	frozen	SW	sweetened
G	gram	TB	tablespoon
GD	good	TID	tidbit
GIB	giblets	TOT	total
GLU	glucose	TR	trimmed
GR	grade	UNCKD	uncooked
HP TSP	heaping teaspoon	UNPKD	unpacked, not packed
HV	heavy	UNSP	unspecified
HYD	hydrogenated	UNSW	unsweetened
IU	international units	VEG	vegetable
L	litre	VIT	vitamin
LG	large	W	with
LIQ	liquid	WGHT	weight
LM	lean meat only	WED	wedge
LMF	lean meat and fat	WH	whipped
LT	light	W/OUT	without
LVS	leaves		

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TABLE 3 Continued

	Definition
heaping teaspoon	- refers to ordinary teaspoon rather than to standard measuring teaspoon
not packed	- lightly filled measure without pressing down on the food
packed	- maximum amount of food that can be pressed into the measure without altering its physical structure
pared	- skin removed plus some adhering flesh
peeled	- skin removed with a minimum of adhering flesh
MF (BF)	- milk fat (butter fat) content stated on the product label
/	- or
-	- yields
+	- plus or and
&	- and

* Most of these abbreviations and definitions are the same as those used in the Canadian Nutrient File (CNF, 1985).

Appendix G

Measures and Conversion Factors for Food Portions

All nutrient values in the data base are for edible portions of foods in 100 g amounts except for nutrient supplements (Food Group #40) which are for one unit (eg., one pill, one capsule, one tablespoon of protein powder). Using conversion factors this information can be accessed for calculations of weighed portions of foods, of common portions, or of household measures. Up to 10 conversion factors that correspond to various portions or measures are included with each food. Choices of measures or portions are outlined in Table 4.

Conversion factors are used to provide nutrient values for specific weights (grams) of foods in various household measures, package sizes and serving sizes suggested by the food company or selected on the basis of Canada's Food Guide portion sizes or others in common use. They do not necessarily represent amounts actually consumed.

Conversion factors that represent both customary measures and metric measures are available.

If "banana, yellow, raw" is selected (Food Group #10, Fruit), for example, 10 measures and conversion factors appear on the screen. The term "medium" represents a banana that is 22 cm long x 3.6 cm in diameter that weights 175 g AP (as purchased) and equals 114 g EP (edible portion) but the only information on the screen in addition to the term "medium" is the conversion factor of 114 which represents the weight of the edible potion of the 175 g banana. By selecting one unit of medium 114/100th of the amount of each nutrient will be added to a subject's file. If it were known that the subject had consumed 114 g banana (edible portion) it would be equally suitable to enter 1.14 x 100 g portion or measure. If it were known that the subject had consumed 175 g banana (as purchased), the edible portion must be calculated from this information before making the selection because all nutrients are for edible portions of food.

Additional information about the measure codes is in the section entitled "Notes on Measure Codes". To aid in determining yields and portion sizes, as well as weights in relation to dimensions, several other sources can be consulted (CNF, 1988; USDA, 1976-1987; 1977; 1979).

TABLE 4

Measure Codes Used to Designate Weights, Common Portions and Household Measures in the Nutrient Data Base

Measure Code	Portion or Measure
1	fluid ounce
2	cup (237 ml)
5	tablespoon (15 ml)
6	teaspoon (5 ml)
10	small
11	medium
12	large
13	scoop (1/2 cup or 118.5 ml)
14	scoop (1/3 cup or 79 ml)
16	average
21	cube
22	can or bottle
29	jar
30	number (as in one fruit, dinner, entree, cookie, cake, pie, cracker, pita bread)
35	package or container (as for yogurt, ready-to-eat cereals)
36	pat
38	piece
42	serving or portion
44	slice
46	stalk or spear or sprig
47	stick
48	strip
60	wedge or sector
70	ounce
75	edible portion (E.P.) per kilogram as purchased (A.P.) (Factor 4, CNF*)
97	poultry meat portion from 500 g ready-to-cook whole poultry
98	100 g
99	100 ml (Factor 1, CNF*)

* Canadian Nutrient File Factors 1 and 4.

Notes:

1. Numbers do not appear on the computer screen only descriptive terms and conversion factors appear.

2. Factors 2 and 3 of the CNF provide the nutrients in various edible portions which have been incorporated into the above measure codes, whenever possible. Factors in the CNF are referred to as portion size conversion factors (CNF, 1988. Canadian Nutrient File Users Guide, Health and Welfare Canada). These two factors are being added to the data base and will be available in the near future.

3. See "Notes on Measure Codes" for further details on measure code equivalents for each food group.

Appendix G

Nutrient Values

A list of the 46 nutrients included in the data base is in Table 5. Nutrients are more or less grouped together by type. The energy produced by the food appears first in both kilocalories commonly known as calories and in kilojoules (kJ). The energy producing nutrients appear in the following order: protein, fat, and carbohydrate, but immediately following total fat are: saturated fat, monounsaturated fat, polyunsaturated fat, oleic acid, linoleic acid, and cholesterol, and immediately following carbohydrate are: fibre, dietary fibre, total sugar, individual sugars, and reducing sugar. Next are vitamins in alphabetical order and minerals in alphabetical order.

Not all foods have values for all nutrients. For example, those foods selected from the Canadian Nutrient File have no values for sugars unless they have been added from another source. Those foods in the original Kellogg Data Base have had all values added for food energy in kilojoules, vitamin A in retinol equivalents, niacin in niacin equivalents, and vitamin D in mcg, and some values added for copper, manganese, vitamin E and biotin. Nutrient values from food companies, in general, were quite limited. They were those provided in significant amounts by that food. For some combination foods, in particular, only macronutrients were available. Many nutrient values, however, have been added from other sources or imputed from a recipe.

A zero can denote an absence of the nutrient or lack of reliable data for a constituent believed to be present in a measurable amount. A blank means no nutrient information is available from the source at the present time. Brackets around a value identify an imputed value. Steps are being taken to change those zeros that indicate a lack of reliable data to blanks and to complete the nutrient profile for each food with imputed nutrient values or selected values from other sources. As of August, 1989, just prior to the merging of the data base with the 1988 Canadian Nutrient File, the completeness of the data base was as shown in Table 6.

Source Identification of Nutrient Values

Sources of information are documented in a series of master lists of foods. The first number or letter indicates the sources and the remaining three to six numbers and/or letters identify the company number, page number or food item number depending on how the food items were identified in the original source. Additional nutrient data added for some nutrients cannot be identified through the source code. The source codes are listed in Table 7 and the contributing companies in Table 8.

TABLE 5

Nutrients in the Data Base

Food energy (kcal)*
Food energy (kJ)
Moisture (g)
Protein (g)
Total fat (g)
Saturated fatty acids (g)
Monounsaturated fatty acids (g)
Polyunsaturated fatty acids (g)**
Oleic acid (g)
Linoleic acid (g)
Cholesterol (mg)
Carbohydrates (g)
Fibre, crude (g)
Dietary fibre (g)
Total sugar (g)
Fructose (g)
Glucose (g)
Lactose (g)
Maltose (g)
Sucrose (g)
Reducing sugar (g)
Biotin (mcg)
Folacin (mcg)
Niacin (mg)
Niacin (NE)
Pantothenic acid (mg)
Riboflavin (mg)
Thiamin (mg)
Vitamin A (IU)
Vitamin A (RE)
Vitamin B6 (mg)
Vitamin B12 (mcg)
Vitamin C (mg)
Vitamin D (IU)
Vitamin D (mcg)
Vitamin E (mg alpha-tocopherol)
Calcium (mg)
Copper (mg)
Fluoride (mg)
Iron (mg)
Magnesium (mg)
Manganese (mg)
Potassium (mg)
Phosphorus (mg)
Sodium (mg)
Zinc (mg)

* Designated as calories in the printouts
** Abbreviated as PUFA (g) in the present data base. Referred to as F/S or P/S in various older documents associated with the previous versions of the data base.

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TABLE 6

Completeness of the Nutrient Data Base

Nutrient	Data base before merger with 1988 Canadian Nutrient File (% complete)	Data base after merger with 1988 Canadian Nutrient File (% complete)
Food energy (kcal)	100	100
Food energy (kJ)	100	100
Protein (g)	99+	
Total fat (g)	99	
Saturated fatty acids (g)	91	
PUFA (g)	89	
Carbohydrates (g)	99+	
Dietary fibre (g)	97	
Total sugar (g)	89	
Sucrose (g)	84	
Folacin (mcg)	93	
Niacin (mg)	96	
Niacin (NE)	96	
Pantothenic acid (mg)	87	
Riboflavin (mg)	98	
Thiamin (mg)	98	
Vitamin A (IU)	93	
Vitamin A (RE)	91	
Vitamin B6 (mg)	90	
Vitamin B12 (mcg)	95	
Vitamin C (mg)	96	
Vitamin D (IU)	97	
Vitamin D (mcg)	97	
Calcium (mg)	98	
Iron (mg)	98	
Magnesium (mg)	89	
Potassium (mg)	96	
Phosphorus (mg)	97	
Sodium (mg)	96	
Zinc (mg)	100	
Cholesterol (mg)	74	

Notes:
1. Completeness of the data base for nutrients following merger with the 1988 Canadian Nutrient File (CNF) has not yet been calculated. Checking the User and Programmer's Guide for the CNF (1988) will give an indication of completeness for each nutrient, except sugars.

2. Completeness of the data base for nutrients not listed has not been calculated. Whereas additional work has been done to complete the nutrient information for the nutrients listed above, not much has been done for individual sugars, oleic and linoleic acids, copper, manganese, fluoride, vitamin E, and biotin. Checking the User and Programmer's Guide for the CNF (1988) will give an indication of completeness for each nutrient except individual sugars.

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TABLE 7

Codes for Identifying the Main Source of the Nutrient Values*

Source Letter or Number	Food Item Identifier	Source
0 to 9	Unable to decode	Original Kellogg Data Base
C	Numbers are the same as those in the CNF	Canadian Nutrient File (CNF)
E		Calculated values (USDA, 1966).
F	Food number as published	HWC, 1985
L	Page number and food letter	Leveille et al., 1983
M	Company number (see Table 6)	Manufacturer or food company supplying the nutrient data
N	Code number which identifies the food	HWC, 1979
P	Page number	Pennington and Church, 1985
U	Food item number which includes the handbook number and the food number	USDA, 1976-1987; 1986
W	Food item number	Paul and Southgate, 1978

* If the main source did not have a value for a nutrient a value from another source was sometimes added. For example, nutrient values for Stouffer's Lean Cuisine dinners were supplied by the manufacturer so the code M was used but total sugars were added from Pennington and Church (1985). Additional sources are noted on the input forms.

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TABLE 8

Food Companies Contributing to the Data Base Revision*

Food Company	Code Number
Associated Biscuits - (Dad's Cookies, Peak Freans)	022
The Borden Company Ltd. - (Realemon, Wyler's, Snow's, Old London)	006
Cadbury Schweppes Powell Inc. - (Welch's, Ocean Spray, Cadbury's Schweppes)	008
Campbell Soup Co. Ltd. - (Campbell's, Swanson, Pepperidge Farm, Le Menu)	009
Canadian Canners Ltd. - (Aylmer, Del Monte)	011
Carnation Inc.	016
Catelli Ltd. - (Laura Secord, Milk Mate, Catelli, Habitant)	017
City of Edmonton	081
Crush Canada Inc.	021
Dare Foods Ltd.	023
E.D. Smith & Sons, Ltd.	053
Effem Foods Ltd. - (Uncle Ben's, Mars)	024
Fraser Valley Milk Producers Cooperative Association - (Super Socco)	025
General Foods Ltd.	027
General Mills Canada Inc.	028
H.J. Heinz Company of Canada Ltd.	030
Heritage Foods - (Cheemo)	031
Interbake Foods Ltd. - (Paulin's, McCormicks)	034
Jorden & Ste. Michelle Cellars Ltd.	035
Kellogg Salada Canada Inc. - (Kellogg's, Eggo, Shirriff, Mrs. Smith, Farmhouse, Salada)	036
Kraft Ltd.	037
Libby, McNeill & Libby of Canada	038
Magic Pantry Foods Inc.	041
McCain Foods Ltd.	043
Nabisco Brands Ltd. - (Christie's)	045
Nanton Spring Water Co., Ltd.	047
National Sea Products Ltd. - (Highliner)	048
Nestle Enterprises Ltd. - (Nestle, Stouffer's)	049
Nippon Suisan (Canada) Limited	050
Palm Dairies Ltd.	052
Proctor and Gamble Inc. - (Duncan Hines)	056
Rich Products of Canada Ltd.	060
J.M. Schneider Inc.	063
Westvale Foods Ltd.	067

* In the data base, manufacturer or brand names are at the end of a food name, separated from it by a hyphen. Some brand names of companies are in brackets following the food company name above. Having the manufacturer's name identified with the food has created some difficulties for users who want to give food lists to subjects because substitutes imply that a subject ate a different brand from what was actually consumed, eg., printout may say Palm yogurt when the subject actually ate Lucerne because the user made the best substitute based on fat level.

Appendix G

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August 27, 1985
Revised June 30, 1987; August 31, 1989

Appendix G

APPENDIX H

Nutrition Assessment Handout

NUTRITION ASSESSMENT

Based on Your Three-Day Food Record

Name	: CINDY VIGER
Sex	: Female
Age	: 28 years
Weight	: 52 kg (115 lbs)
Height	: 158 cm (5 ft 2 in)

Food Record Dates
Oct 4 88

The presentation of the information on the nutrient content and adequacy of your diet is similar to that in the proposal put forward by Health and Welfare Canada (1) for nutrition labelling of foods to allow you to compare your intake with the nutrition information on food labels as it becomes available.

(1) Information Letter No. 713. July 24, 1986

Average Daily Intake of Selected Nutrients

Nutrient			Your average daily intake	Intakes currently suggested
Energy			206 kcal 862 kJ	(Dependent on individual)
Protein			9.3 g	(See %RNI below)
Fat			0.9 g	(See balance below)
Carbohydrate			48.3 g	(See balance below)
	Sugars		24.5 g	(See sugar intake below)
		Sucrose	8.2 g	
		Fructose	4.7 g	
		Glucose	4.8 g	
		Lactose	6.0 g	
		Unclassified	0.0 g	
	Dietary Fibre		9.3 g*	(25 to 40 g)
Sodium			0.3 g	(0.5 g)
Potassium			0.7 g	(1.6 g)

How Adequate Was Your Nutrient Intake

Your intake as a percentage of recommended daily nutrient intake (RNI) (1)			
Protein	24%*	Folacin	39%*
Vitamin A	12%*	Vitamin B12	25%*
Vitamin D	50%*	Calcium	30%*
Vitamin C	110%	Phosphorus	56%*
Thiamin	100%	Magnesium	63%*
Riboflavin	32%*	Iron	34%*
Niacin	42%*	Zinc	28%*
Vitamin B6	234%		

How Well Balanced Was Your Energy Nutrient Intake

Energy intake from various nutrients Source of energy	Your percentages	Percentages currently suggested
Protein	16%	(8 to 15%)
Fat	3%	(15 to 35%)
Carbohydrate	81%	(50 to 60%)

How Much Sugar Was Consumed

Energy intake from sugars Source of energy	Your percentage	Current suggestion(1)
Sugars	41%*	(Keep low in relation to other carbohydrates)

* See Page 3.

(1) Health and Welfare Canada. 1983. "Recommended Nutrient Intakes for Canadians". Ottawa K1A 0S9

Appendix H

Your dietary fibre intake may be too low. Good sources of dietary fibre are bran cereals, shredded wheat, rolled oats, whole grain breads, baked beans, cooked dried peas, beans and lentils, fruits, vegetables, and nuts.

Your protein intake may be too low. Good sources of protein are meat, poultry, fish, eggs, cooked dried peas, beans and lentils, nuts, seeds, peanut butter, milk, cheese and yogurt.

Your folacin intake may be too low. Good sources of folacin are liver, kidney beans, spinach, asparagus, broccoli, beets, cabbage, corn, lima beans, parsnips, green peas, sweet potatoes, oranges, orange juice, and cantaloupe.

Your vitamin A intake may be too low. Good sources of vitamin A are liver, carrots, pumpkin, spinach, sweet potato, broccoli, apricots, winter squash, tomatoes, cantaloupe, peaches, eggs, butter and margarine.

Your vitamin B12 intake may be too low. Good sources of vitamin B12 are meat, poultry, fish, eggs, milk and cheese.

Your vitamin D intake may be too low. Good sources of vitamin D are milk, salmon, sardines, shrimp, liver, and egg yolk.

Your calcium intake may be too low. Good sources of calcium are milk, firm cheese, yogurt, canned sardines and salmon with bones, spinach, broccoli, nuts and sesame seeds.

Your phosphorus intake may be too low. Good sources of phosphorus are meat, poultry, fish, eggs, milk, yogurt, and cheese.

Your magnesium intake may be too low. Good sources of magnesium are nuts, cooked dried beans, peas and lentils, whole grain breads and cereals, broccoli, spinach, and seafoods.

Your riboflavin intake may be too low. Good sources of riboflavin are meat, liver, heart, milk, yogurt, and enriched breads and cereals.

Your iron intake may be too low. Good sources of iron are beef, lamb, veal, eggs, liver, heart, dried fruits, apricots, cooked dried peas and beans, nuts, green peas, green leafy vegetables, and whole-grain breads and cereals.

Your niacin intake may be too low. Good sources of niacin are meat, poultry, fish, eggs, cooked dried peas, beans and lentils, nuts, seeds, peanut butter, cheese, milk, yogurt, and whole grain and enriched breads and cereals.

Appendix H

Your zinc intake may be too low. Good sources of zinc are meat, poultry, shellfish, nuts, milk, eggs, and whole grain breads and cereals.

Not having met 100% of the Recommended Nutrient Intakes does not necessarily mean an inadequate intake because the RNI is set to allow a margin of safety. To maintain a low chance of an inadequate intake, however, you should aim to meet the RNI.

Your sugar intake may be too high. Try limiting your intake of candy, chocolate bars, cakes, cookies, ice cream, pies, soft drinks except diet drinks, fruit-flavoured drinks, flavoured milk, sweetened yogurt, sweetened fruit juices, canned fruit, dried fruit, jam, honey, chewing gum, and sweetened cereals.

Appendix H

Subject : CINDY VIGER File Name :
Weight : 52.3 kg Height : 158.0 cm Sex : Female Age : 28
Day 1 of 1 Oct 4, 1988

Time	Amount		Item Name
7:00	0.500 cup	(123.000 g)	MILK, SKIM
7:00	0.500 cup	(12.405 g)	GRAPE NUT FLAKES - POST
7:00	0.250 cup	(21.262 g)	ALL BRAN - KELLOGG'S
7:00	1.000 small	(90.000 g)	ORANGE, RAW
7:00	0.100 100 ml	(6.974 g)	RAISINS, GOLDEN SEEDLESS

Appendix H

APPENDIX I

Girth Measurement Protocol

The following seven girth measurements were taken:

1. Arm girth, relaxed

With the subject standing erect and the relaxed arm hanging by the side, the perimeter distance was taken between the top of the olecranon and acromion process.

2. Arm girth, flexed

The right arm was raised to a horizontal position and the subject asked to "make a muscle" by flexing the bicep muscle. The measurement was taken at the mid-point between the olecranon and acromion process.

3. Chest girth

The arms were abducted to a horizontal position, and the measurement then taken at the level of the mesosternale (mid-line of the sternum) at the end of a normal expiration.

4. Waist girth

The measurement was taken at the level where there was a noticeable narrowing (minimum girth) of the unclothed abdomen, and at the end of a normal expiration.

5. Gluteal girth

The subject stood relaxed with feet together. The tape was placed around the hips and the measurement taken at the maximal gluteal protrusion and anteriorly at the level of the symphysis pubis.

6. Thigh girth

With the feet shoulder width apart and weight equally distributed on both feet the tape was positioned around the top the right thigh just below the gluteal furror.

7. Calf girth

With the subject sitting in a chair with the knee flexed at a 90^{o} angle the "unweighted" calf measurement was taken at its maximal protrusion.

APPENDIX J

Skinfold Measurement Protocol

The procedures used for the five skinfold measurements taken is outlined below:

1. Tricep skinfold

With the arm relaxed at the subject's side a vertical skinfold was taken on the posterior surface of the arm, mid-way between the tip of the acromion and olecranon process.

2. Bicep skinfold

The skinfold was lifted vertically on the anterior surface of the upper arm at the mid-point between the olecranon and acromion process.

3. Subscapula skinfold

A downwards oblique (45°) skinfold was taken approximately 1 cm distally to the inferior angle of the scapula.

4. Iliac-crest skinfold

The skinfold measured 3 cm superior to the iliac crest at the mid-line of the body so that the fold ran anteriorally downwards. The subject's right hand was placed on her left shoulder to keep her arm from interfering with the measurement.

5. Calf skinfold

With the subject seated and the leg flexed at a 90° angle at the knee, a vertical skinfold along the mid-line on the medial calf was taken at the estimated greatest circumference.

APPENDIX K

Physical Activity Questionnaires and Evaluation

PHYSICAL ACTIVITY QUESTIONNAIRE

DATE OF INTERVIEW _____ INTERVIEWER___Cindy Viger___

SUBJECT'S NAME:_____

1. Would you describe for me your past recreational and athletic activities from about age 15? Would you consider yourself to have been quite active?

2. Would you describe your present recreational and athletic activities in terms of the type of activity, the frequency, duration and level of intensity?

3. What types of activities have you been involved in over the last 12 months?

4. Comparing your activity in your spare time during the last 12 months with 3-4 years ago would you say you are more active, less active or about the same?

5. In the past year, did you stop doing any physical activity in your spare time? What was the main reason for stopping?

6. With whom do you usually do your physical acitivites in your spare time?

7. Where do you usually do you physical activities in your spare time?

8. Are there any exercise or sports activities you would like to or plan to start in the next year?

9. Does your job require much activity? If,so, what?

10. Do you do much housework and/or yardwork around your home?

11. Other comments:

Appendix K

Date _____

PHYSICAL ACTIVITY QUESTIONNAIRE

BONE RESEARCH UNIT
10-102 Clinical Sciences Building
University of Alberta

We are interested in knowing how physically active you have been over the last 12 months. To help you describe your activities to us, two tables are provided. One table is for you to list and describe the "exercise-type" activities you have been doing (e.g., walking, golfing); the other is for you to describe the "day-to-day" activities you engage in (e.g., housework, gardening). In addition to **what** activities you did, we are also interested in **how often** you did them (i.e, everyday, once a week), **how long** you spent doing them each time (30 mins, 2 hrs), and the **length of time** you were involved in them (i.e., all year, winter only, a 6-week program). The tables should actually help you provide this information.

EXERCISE-TYPE ACTIVITIES

A list of "exercise-type" activities is provided below. Review the list; select those that you have been involved in over the past year; write them into the table; and then do your best to describe your involvement them. If you find that an activity (or some activities) that you have been doing is not included in the list, add it (or them).

aerobics • aquatic exercises • badminton • bicycling (stationary or outside) • bowling • calisthenics • canoeing • cross-country skiing • dancing (square, folk, social) • downhill skiing • golfing (state whether you walked or used a golf cart) • jogging • judo • karate • sailing • skating • softball • stretching • swimming • tai kwon do • tennis • walking • weight-lifting

ACTIVITY	HOW OFTEN?	FOR HOW LONG (on average)?	LENGTH OF TIME	COMMENTS
eg. walking	*every evening*	*40 minutes*	*all year*	

Appendix K

DAY-TO-DAY ACTIVITIES

This table should be used to list and describe the day-to-day activities you did, at home or at work. "Day-to-day" activities are those done on a regular basis, at home or at work, that require you to exert some effort to complete them. Anything that requires you to be on your feet for an extended amount of time; or places a substantial force on your bones, joints or muscles (i.e.,walking or lifting) should be included here. Again, a list of such activities is provided for you to select from. Remeber, if you cannot find some that you have been doing, just add them.

doing laundry * gardening * preparing and/or cleaning up after meals * lawn mowing * grocery shopping * making beds * mopping or sweeping floors * raking leaves * shoveling snow * stair-climbing (a minimum of 10 stairs) * vacuuming * washing floors * window shopping * employed full-time at a job that requires you to be on your feet a good part of the day * employed part-time at a job that requires you to be on your feet * involved in a hobby that requires some physical exertion

ACTIVITY	HOW OFTEN?	FOR HOW LONG (on average)?	LENGTH OF TIME	COMMENTS
eg. gardening	*3 times a week*	*40-60 minutes*	*spring, summer, fall*	

When you compare your activity level during the last 12 months to that of the year before this one, are you:

_____ more active _____ less active _____ same

When you compare your activity level during the last 12 months to that of the year before this research started, are you:

_____ more active _____ less active _____ same

Appendix K

PAQ EVALUATION

Date 1 _____ **Date 2** _____ **Date 3** _____

Rating 1 _____ **Rating 2** _____ **Rating 3** _____

Score each of the following statements "1" if it is **true**.

Baseline	Year 2	Year 3	
___	___	___	engages in regular household chores daily (i.e., meal preparation, bed making) and/or weekly (i.e., grocery shopping, laundry sweeping/vacuuming).
___	___	___	engages in stairclimbing daily (minimum of 10 stairs, 3x a day).
___	___	___	engages in seasonal chores around the home at least once a week (i.e., shovelling snow , gardening or yard work).
___	___	___	engages in an "active" hobby or is employed at a part-time job at least once a week (i.e., either of which should require her to be on her feet for an extended period or place a substantial force on the bones, joints or muscles).
___	___	___	is employed full-time outside the home at a job that requires her to be on her feet a lot of the day.
___	___	___	engages in low-moderate intensity exercise activities (i.e., yoga).

Score either of the following statements "2" — if **true**.

___	___	___	engages in moderate-high intensity exercise activities (i.e.,swimming, biking, weight-lifting, walking, jogging, aerobics, tennis, skiing) occasionally (i.e., less than 3 times a week or only at certain times of the year) for ≥ 30 minutes each time ...
			OR
___	___	___	engages in the same moderate-high intensity exercise activities ≥ 3 times a week but for <30 minutes each time.

Appendix K

Score the following statement "7" if it is true.

____	____	____	engages in moderate-high intensity exercise activities (i.e ,swimming, biking, weight-lifting, walking, jogging, aerobics, tennis, skiing) regularly (i.e., ≥ 3 times a week), throughout the year, for ≥30 minutes each time.
____	____	____	**TOTALS**
14	14	14	

1 - **sedentary** (does little that involves physical activity except for household chores) daily

1-4

2 - **active** (is on feet a lot during daily living activities and/or some sports or active hobbies) involved in

5-7

3 - **very active** (does vigorous physical activity >3x a week living activities) besides daily

7-14

Appendix K

APPENDIX L

General Weight-lifting Information

HAND-WEIGHT EXERCISES

REMEMBER: always lift the weights in a controlled fashion. Concentrate on the activity and always maintain a fluid motion.

EXERCISE #1 WRIST CURLS

Positioning
- sit close to the edge of your chair and bend forward, resting your forearms on your thighs.
- your feet should be flat on the floor and about shoulder width apart.
- with your working arm (forearm) on your thigh, place your free-hand around the wrist of your working hand for extra support.
- with the palm of your working hand facing up-wards, grasp the hand-weight in the middle of its length.

The Movement
- curl wrist, bringing the weight up, towards the forearm.
- lower the weight down slowly until you feel the stretch in your wrist and forearm.

EXERCISE #2 WRIST ROTATIONS

Positioning
- sit close to the edge of your chair and bend forward, resting your forearms on your thighs.
- your feet should be flat on the floor and about shoulder width apart.
- if you feel more comfortable you can also support your forearm with your free-hand.
- with your palm facing up-wards, grasp the hand-weight in the middle of its length.

The Movement
- gently rotate the weight through 180^{o} so that the palm of your hand is now facing the floor, then slowly return to the starting position.

EXERCISE #3 WRIST CIRCLES

Positioning
- sit close to the edge of your chair and bend forward, resting your forearms on your thighs.
- your feet should be flat on the floor and about shoulder width apart.
- place the working arm (forearm) on your thigh.
- with your palm facing up, grasp the hand-weight at one end of its length.

The Movement
- with your forearm remaining in contact with your thigh pretend you are drawing a large circle with the weight, repeat the movement in the opposite direction.

EXERCISE #4 **BICEP CURLS**

Positioning
- sit back in the chair with your back pressed comfortably up against the back of the chair.
- sit to one side of the chair so that your arm hangs down by your side without touching the chair (your chair cannot have arms).
- grasp the hand-weight in the middle of its length.
- let your arm hang straight down at your side, with palm towards you.

The Movement
- bend your arm at the elbow so it moves toward your shoulder.
- as the weight approaches your shoulder, rotate your wrist a quarter turn so that your palm is facing your shoulder.
- bring the weight slowly down until your arm is again in the fully extended position.

EXERCISE #5 **TRICEP EXTENTION**

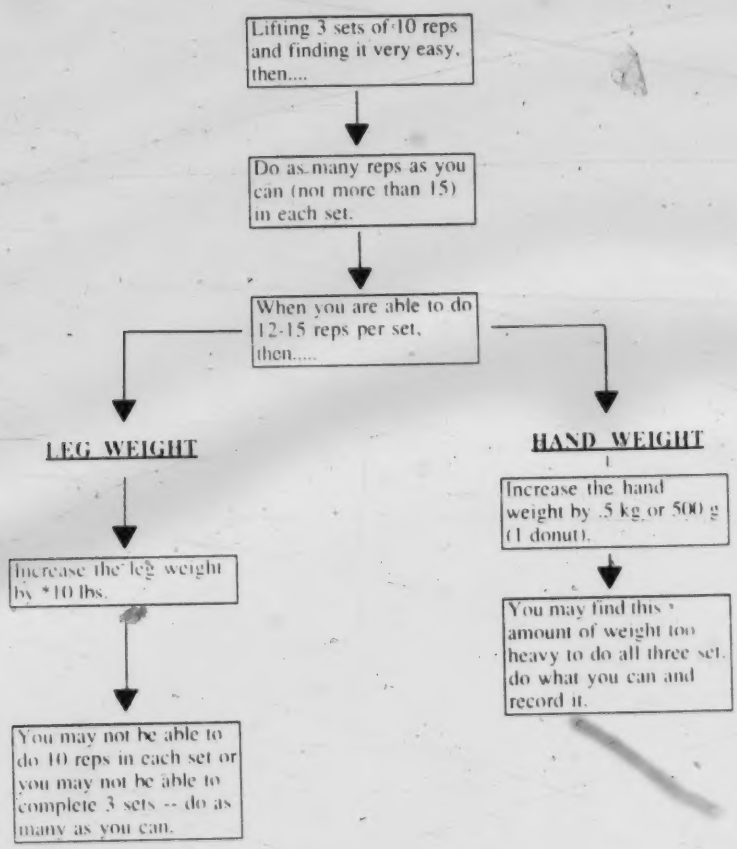
Positioning
- sit back in the middle of the chair with your back pressed comfortably up against the chair
- grasp the hand-weight in the middle of its length and extend your arm straight up above your head.
- keep your bicep as close to the side of your head as possible.
- place your free hand on your elbow to stabilize it.
- keep the elbow in the same position throughout the exercise.
- look straight ahead.

The Movement
- bend elbow allowing the weight to be slowly lowered behind your head.
- then return to the starting position by extending your arm above your head again.
- you should feel a stretch in your tricep area.
- maintain control of the weight throughout the movement, if your are unable to then reduce the amount of weight.

NOTE: This picture does not represent the exact exercise you are performing. Remember you will be using your free hand as a support for your elbow. Your elbow should remain in the same position throughout the exercise.

WEIGHT INCREMENTS DURING WEIGHT-LIFTING

BONE RESEARCH UNIT
10-105 CLINICAL SCIENCES BUILDING
EXERCISE GROUP


Lifting 3 sets of 10 reps and finding it very easy, then....
Do as many reps as you can (not more than 15) in each set.
When you are able to do 12-15 reps per set, then.....
LEG WEIGHT
Increase the leg weight by *10 lbs.
You may not be able to do 10 reps in each set or you may not be able to complete 3 sets -- do as many as you can.
HAND WEIGHT
Increase the hand weight by .5 kg or 500 g (1 donut).
You may find this amount of weight too heavy to do all three set. do what you can and record it.

* You may not be able to increase by 10 lbs., so try either a 5 or 3 lb weight.

BONE RESEARCH UNIT 3/1989

Appendix L

APPENDIX M

Monthly Activity Forms

ACTIVITY FORM FOR NOVEMBER

DATE	WRIST AND ARM EXERCISES								
	WRIST EXERCISES			BICEP CURLS			TRICEPS		
	No. of Sets	No. of Reps	Amt. of Wt.	No. of Sets	No. of Reps	Amt. of Wt.	No. of Sets	No. of Reps	Amt of Wt

BONE RESEARCH UNIT

NAME_____

ACTIVITY FORM FOR JUNE

DATE	LEG PRESS		COMMENT
	# OF SETS/ # OF REPETITIONS	AMOUNT OF WEIGHT	

BONE RESEARCH UNIT

Appendix M

APPENDIX N

Pre-exercise Warm-up Routine

WARMING - UP

Warm-up exercises prior to weight-lifting

The illustrations used in this warm-up sheet have been taken from Fit All Over, a catalogue of exercises, by S. Main, G.W. Stewart and R. Bradshaw (1984), and Stretching, by B. Anderson (1979).

The reason for "warming-up" prior to exercise is to prepare your body for exercise by increasing heart rate and body temperature, also it helps to help lubricate joints. By doing the following set of exercises prior to your weight-lifting program, this will help to prevent injury such as a pulled or strained muscle. Your warm-up should take about 10 minutes.

TILT

Tilt head from side to side.

TURN

Start... face centre

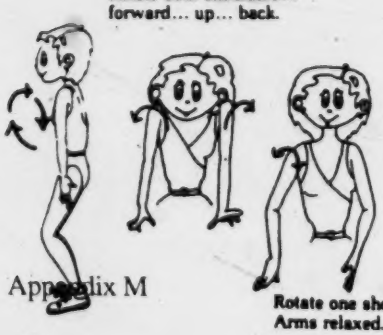
Look right, and centre... left, and centre.

ROLL

Gently press chin on chest when the head is forward.

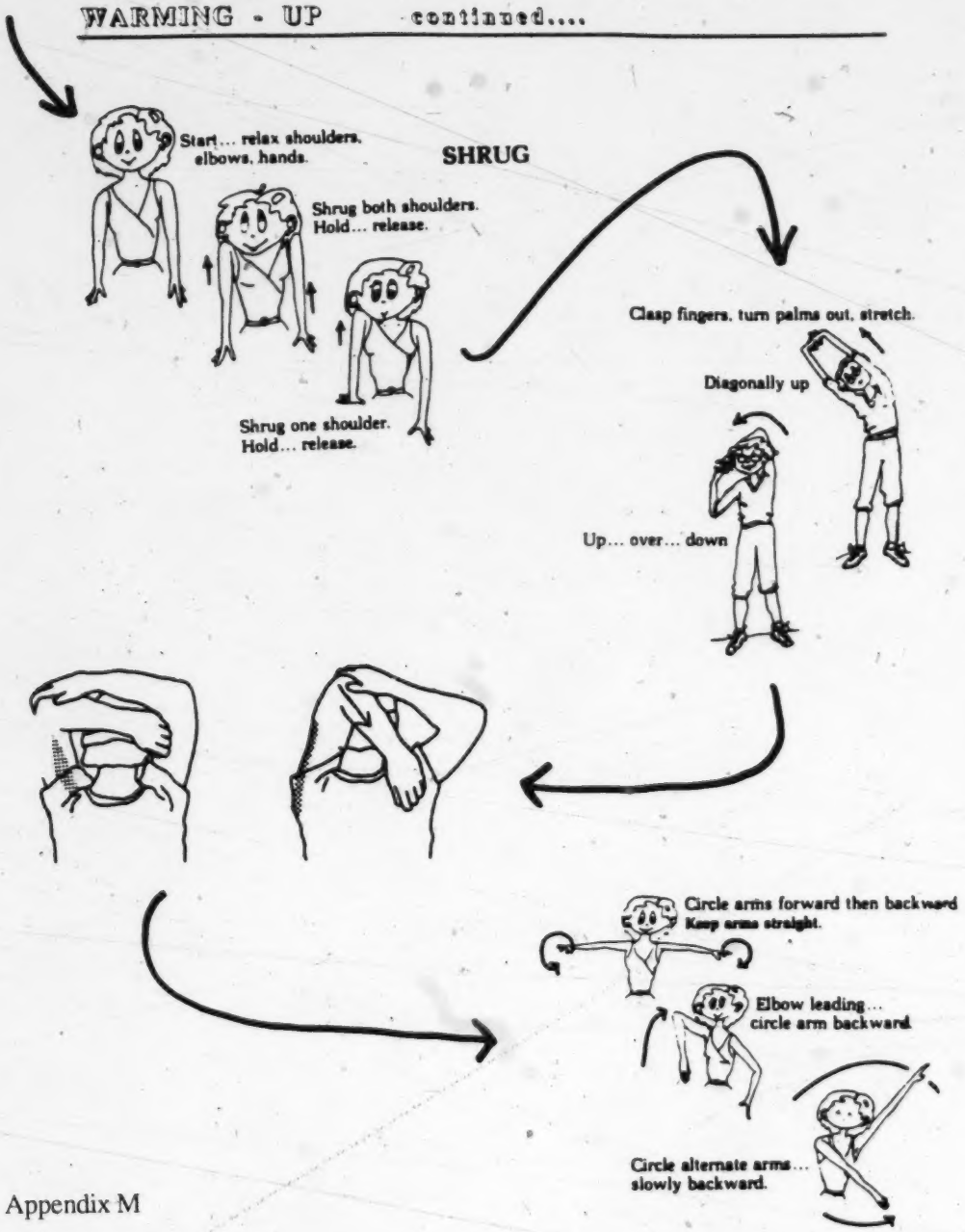
Do not roll head backward.

Rotate both shoulders... forward... up... back.



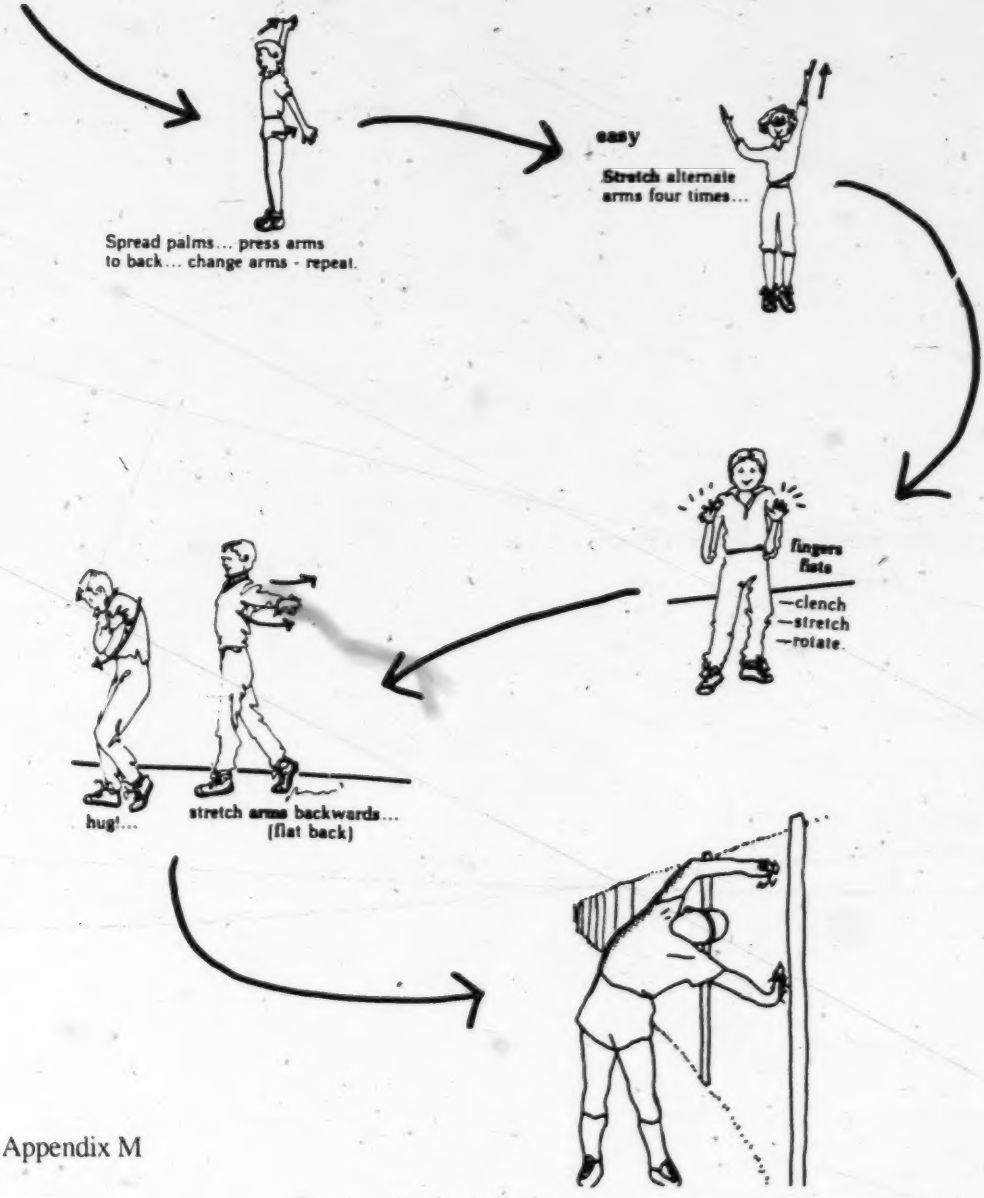
Rotate one shoulder. Arms relaxed.

WARMING - UP continued....


Start... relax shoulders, elbows, hands.
SHRUG
Shrug both shoulders. Hold... release.
Shrug one shoulder. Hold... release.
Clasp fingers, turn palms out, stretch.
Diagonally up
Up... over... down
Circle arms forward then backward
Keep arms straight.
Elbow leading... circle arm backward
Circle alternate arms... slowly backward.

Appendix M

WARMING - UP continued....



Appendix M

WARMING - UP continued....

HIP CIRCLES

Use a chair for balance.

Swing leg... backward and forward.

Do ankle rotations while standing.

Rotate ankle/foot... in both directions.

'ST ROTATIONS

not bend backwards.

Lunge right... stay low and shift through centre... to the left.

APPENDIX O

Attrition

Exercise Group

Immediately after the subjects had been randomly assigned to the Exercise and Control groups, it was determined that 3 subjects were unable to participate for the following reasons:

(1) two subjects found they were unable to fit the exercise equipment into their apartments, therefore were unable to participate in the Exercise group.

(2) another subject traveled too frequently, approximately 4 months per year and therefore unable to maintain the regular exercise program.

All the the above subjects wished to remain in the study and therefore were placed into the Transfer Control group.

Once the exercise program had begun one subject had to discontinue for the following reason:

(1) the subject developed pinpoint hemorrhaging on her arms and shoulders, this condition progressively became worse, spreading over other parts of her body. It was later determined that her family had a history of blood disorders. In consultation with the medical advisor for this study she immediately discontinued the exercise program and shortly after dropped out of the study.

Control Group

Once the study was underway two subjects in the control group "dropped out" for the following reasons:

(1) one subject felt that the dose of radiation given was unhealthy and wish to discontinue the study for this reason.

(2) one disliked completing a food record so much, she stated she would drop out of the study if she had to complete anymore. This subject remained in the study, however, she was placed into the Transfer Control group, and no longer kept food records.

Hormone Replacement Group

Two women dropped out of the HRT group for the following reasons:

(1) one disliked being on hormones and stopped using HRT completely, she was therefore unable to stay in the study as she no longer qualified for any of the treatment groups.

(2) another subject, although allocated to the HRT group, never initiated the use of the hormones as she decided to go the "natural route", therefore she still qualified for the Transfer Control group.